Stereoselective Syntheses of Certain Natural Products and their Analogues from Chiral-pool and Enzymatically-derived Building Blocks

A thesis submitted for the Degree of Doctor of Philosophy of The Australian National University

by

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Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2013-2017 and has not been submitted for examination for any other degree. This thesis by publication is comprised of six journal articles. Wherever possible, established methodologies have been acknowledged by citation of the original publications.

Joshua Buckler

September, 2017

Acknowledgements

First and foremost, I would like to extend my gratitude to my supervisor Professor Martin Banwell. Your enthusiasm and encouragement when things were going well has been inspiring and your patience, wisdom and support when things weren't going so well has been invaluable. I have benefited greatly from your guidance and knowledge during the course of my PhD your passion for chemistry has proven to be infectious.

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Over the past four and a half years I have worked alongside many great people in the Banwell group that have made my experience a pleasant one. Special thanks go to Eric Harris, Jeremy Nugent and Shen Tan who have always been there with encouragement and ideas, both in and out of the laboratory. I would also like to acknowledge the technical staff at the Research School of Chemistry, in particular the Mass Spectrometry team.

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I would also like to thank the Research School of Chemistry, the Australian Research Council and Institute of Advanced Studies for support. I am a grateful recipient of an Australian Postgraduate Award (APA) provided by the Australian Government and this work would have not been possible without this opportunity.

Finally, I am eternally grateful for the love and the support I have had from my family and friends, both here in Australia and at home in New Zealand.

Publications and Presentations

This thesis is submitted in publication format.

The following publications and presentations have resulted from the author's research work carried out during the course of his candidature for the Degree of Doctor of Philosophy.

PUBLICATIONS:

1. Martin G. Banwell, Joshua Buckler, Colin J. Jackson, Ping Lan, Xinghua Ma, Eliška Matoušová and Jeremy Nugent. Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase in *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: London, 2015; Vol. 11, pp 29–50.

2. Martin G. Banwell, Benoit Bolte, Joshua N. Buckler, Ee Ling Chang, Ping Lan, Ehab S. Taher, Lorenzo V. White and Anthony C. Willis. Chemoenzymatic Pathways for the Synthesis of Biologically Active Natural Products *J. & Proc. Royal Soc. New South Wales* **2016**, *149,* 34.

3. Joshua N. Buckler, Ehab S. Taher, Nicolas J. Fraser, Anthony C. Willis, Paul D. Carr, Colin J. Jackson and Martin G. Banwell. The Synthesis of Certain Derivatives and Analogues of (–)- and (+)-Galanthamine and an Assessment of their Capacities to Inhibit Acetylcholine Esterase. *J. Org. Chem*. **2017**, *82*, 7869.

4. Joshua N. Buckler, Brett D. Schwartz and Martin G. Banwell – The Synthesis of Polyfunctionalized, Cyclohexene-Based Chirons from Tartaric Acid. *Heterocycles* **2017**, *1*, 290.
   (Invited submission on the occasion of Professor Masakatsu Shibasaki's 70th birthday).

5. Joshua N. Buckler, Tamaryn Meek, Martin G. Banwell and Paul D. Carr. A Total Synthesis of the Cyclic Carbonate-Containing Natural Product Aspergillusol B from *D*-(–)-Tartaric Acid. *J. Nat. Prod.* **2017**, *80*, 2088.

6. Joshua N. Buckler, Martin G. Banwell, Farzaneh Kordbacheh, Christopher R. Parish, Fernando S. Santiago and Levon M. Khachigian. Developing Neolignans as Pro-Angiogenic Agents: Stereoselective Total Syntheses and Preliminary Biological Evaluations of the Four Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers. *ACS Omega* **2017**, *2*, 7375.

CONFERENCE PRESENTATIONS:

1. **RACI Organic One-Day Symposium | *Poster Presentation***
   Joshua N. Buckler and Martin G. Banwell, *Stereocontrolled Syntheses of GGCE-based Neolignans Displaying Potent Pro-angiogenic Activities,* Canberra, Australia, 11th November 2014.

2. **RACI Organic One-Day Symposium | *Poster Presentation***
   Joshua N. Buckler and Martin G. Banwell, *The Synthesis of Polyfunctionalized, Cyclohexene-Based Chirons from Tartaric Acid,* Sydney, Australia, 30th November 2016.

Commentary on the Contributions of Mr Joshua Buckler to the Six Papers Included in this Thesis by Publication

Publication 1

This is an invited book chapter that was written by Professor Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Buckler. Mr Buckler carried out relevant literature surveys as part of his additional contributions to the preparation of this document.

Publication 2

This is a review article that was written by Professor Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Buckler. Mr Buckler carried out relevant literature surveys as part of his additional contributions to the preparation of this article.

Publication 3

This is a full paper detailing extensive experimental work directed towards the synthesis and biological evaluation of mono- and di-oxygenated derivatives and analogues of the therapeutically significant alkaloid galanthamine. Mr Buckler carried out approximately half (*ca.* 50%) of the experimental work reported in the paper. Mr Ehab Taher carried out the remainder of synthetic chemistry and Mr Nicolas Fraser conducted the docking studies and the biological testing. The reported X-ray crystallographic studies were carried out by the RSC's resident crystallographers Dr Anthony Willis and Dr Paul Carr. In addition, Mr Buckler deduced some of the structures of key compounds produced by Mr Taher. Mr Buckler collated and formatted approximately half of the reported spectral data presented in the Supporting Information document and also wrote approximately half (*ca.* 50%) of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 4

This is a full paper detailing extensive experimental work directed towards the synthesis of homochiral and polyfunctionalised chirons from tartaric acid. Mr Buckler conceived of and then conducted the entirety of the research and laboratory work reported in this article save for the X-ray crystallographic studies that were carried out by Dr Brett Schwartz. In addition, Mr Buckler collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Buckler also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 5

This is a full paper detailing extensive experimental work directed towards the synthesis of the cyclic carbonate-containing natural product aspergillusol B. Mr Buckler conceived of and then conducted the majority (90%) of the research and laboratory work reported in this article save for the X-ray crystallographic studies that were carried out by Dr Paul Carr. Certain aspects of the experimental work were carried out by Ms Tamaryn Meek (a summer scholar in the Banwell Group) who worked under the direct supervision of Mr Buckler. In addition, Mr Buckler collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Buckler also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 6

This is a full paper detailing extensive experimental work detected towards the synthesis of the four stereoisomeric forms of guaiacylglycerol 8-*O*-4′-coniferyl ether. Mr Buckler conducted the entirety of the research and laboratory work reported in this article, save for the biological testing which was carried out by members of Professor Levon Khachigian's lab in at the University of New South Wales in collaboration with Dr Farzaneh Kordbacheh (Parish Group, John Curtin School of Medical Research, ANU). Mr Buckler collated and formatted all of the

reported spectral data presented in the Supporting Information document. Mr Buckler also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Table of Contents

List of Abbreviations

$(M + Na)^+$	molecular ion and associated sodium
°C	degrees Celsius
δ	chemical shift (parts per million, ppm)
μL	microliter(s)
ν_{max}	infra-red absorption maxima (cm^{-1})
18-C-6	18-crown-6
4,5-DAF	4,5-Diazafluoren-9-one
Ac	acetyl
AChE	acetylcholine esterase
AD	asymmetric dihydroxylation
app. t	apparent triplet
BE	binding energy
Bn	benzyl
br	broad region
brsm	based on recovered starting materials
Bu	butyl
ca.	*circa* (approximately)
CDI	1,1′-carbonyldiimidazole
CNS	central nervous system
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*-*N*-diisopropylethylamine
DMADMA	*N,N*-dimethylacetamide dimethyl acetal
DMAP	4-(*N,N*-Dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
DMP	Dess–Martin periodinane

DMSO	dimethylsulfoxide
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
E. Coli	*Escherichia coli*
e.g.	*exempli gratia*
EC	Eschenmoser-Claisen
ee	enantiomeric excess
ent-	enantiomer
ESI	electrospray ionisation (mass spectrometry)
et al.	*et alia* (and others)
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
eV	electron volts
FGF-2	fibroblast growth factor 2
FTIR	Fourier transform infrared spectroscopy
g	gram(s)
GGCE	guaiacylglycerol-8-*O*-4'-coniferyl ether
h	hour(s)
HBr	hydrogen bromide
HMEC	human microvascular endothelial cells
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
i.e.	*id est* (that is)
in situ	in the place (in the reaction vessel)
inter alia	among other things
IR	infrared
J	coupling constant
L	litre
M	mol L^{-1}
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
m/*z*	mass-to-charge ratio
Me	methyl

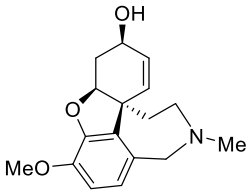
MEK	mitogen-activated protein kinase
mg	milligram(s)
MHz	mega-hertz
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
MS	mass spectrometry
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
ns	not significant
ORTEP	Oak Ridge thermal ellipsoid plot
p	*para*
p-MBnOH	*para*-methoxybenzylalcohol
pH	logarithm of the reciprocal of the hydrogen ion concentration *i.e.* $-\log_{10}[H^+]$
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNB	*para*-nitrobenzoyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
q	quartet
QSAR	quantitative structure-activity relationship
quant.	quantitative yield
Red-Al®	sodium bis(2-methoxyethoxy)aluminum dihydride
R_f	thin layer chromatography retardation factor
rt	room temperature (22 °C)
s	singlet
SAR	structure-activity relationship
sp.	species
t	triplet
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl

TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TIPS	triisopropylsilane
Tf	triflate (trifluoromethanesulfonate)
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMAD	*N*,*N*,*N*',*N*'-tetramethylazodicarboxamide
TMB	tetramethoxybutane
TMSCl	trimethylchlorosilane
Trp	tryptophan
Ts	tosyl (*para*-toluenesulfonyl)
v/v	unit volume per unit volume (ratio)
via	by way of
viz.	*videlicet* (namely)
vs	*versus*
w/v	unit weight per unit volume (%)

Abstract

This thesis is comprised of six scientific articles and is preceded by an overview that contextualises all of this published/submitted work.

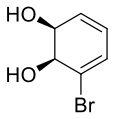
The first section of this thesis is comprised of **Publications 1-3** and is concerned with the synthesis of novel, oxygenated analogues of the natural and non-natural enantiomeric forms of the *Amaryllidaceae* alkaloid galanthamine, a reversible and selective acetylcholine esterase (AChE) inhibitor that is used clinically in the treatment of Alzheimer's disease.



(–)-galanthamine

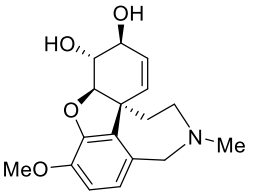
Specifically, **Publication 1** is an invited book chapter that details synthetic approaches to galanthamine and certain analogues pursued by the Banwell Group. It contextualises the strategy employed in preparing oxygenated analogues of galanthamine by the author in latter part of the first section of this thesis.

Publication 2 is an invited review article that showcases the methodologies that have been developed within the Banwell Group for manipulating enzymatically-derived and homochiral *cis*-1,2-dihydrocatechols such as **A** so as to generate a significant range of biologically active natural products.

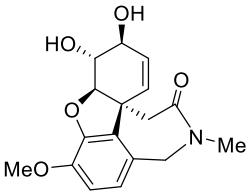


A

Publication 3 describes the synthesis of certain oxygenated derivatives of both (+)- and (–)-galanthamine such as **B** and **C** (and their enantiomers) and the evaluation of these as AChE inhibitors.

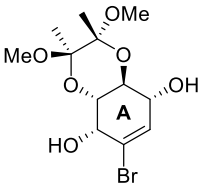


B

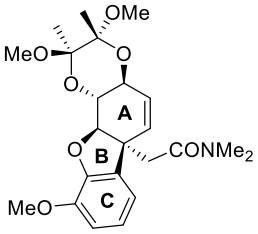


C

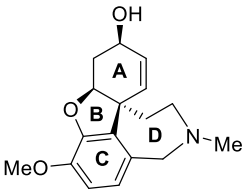
The key intermediate **D** is accessible in both enantiomeric forms, either by manipulation of the aforementioned *cis*-1,2-dihydrocatechol **A** (to give *ent*-**D**) or from *L*-(+)-tartaric acid *via* methodology detailed in **Publication 4**. Intermediate **D** is engaged in a 3-step sequence involving Suzuki-Miyaura cross-coupling, intramolecular Mitsunobu and Eschenmoser-Claisen reactions to rapidly assemble the ABC-ring system of galanthamine, as embodied in compound **E**, with high levels of stereocontrol.



D

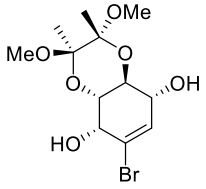


E

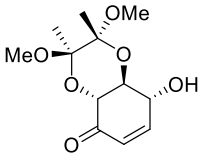


(–)-galanthamine

The second section of this thesis is comprised of **Publications 4** and **5**. These detail the synthesis of chiron **F** and its enantiomer from *L*-(+)- and *D*-(–)-tartaric acid, respectively, and their elaboration into various natural product scaffolds.



D

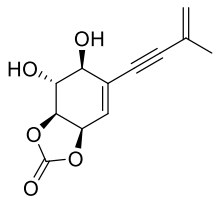


F

Specifically, **Publication 4** describes the preparation of chiron **F** in 6 steps from *L*-(+)-tartaric acid *via* esterification/1,2-diacetal formation, one-pot DIBAL-H reduction-Grignard reagent addition, ring closing metathesis, oxidation and diastereoselective reduction reactions. Compound **F** is itself elaborated to diol **D** through bromination, reduction and Mitsunobu inversion processes. Chiron **D** is

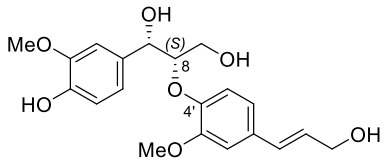
the enantiomer of a key intermediate described in **Publication 3** that is used to produce oxygenated analogues of (–)-galanthamine.

Publication 5 further demonstrates the utility of these new chirons in total synthesis by employing *ent*-**F** [prepared from *D*-(–)-tartaric acid] as a key intermediate in the first total synthesis of the structurally unusual natural product aspergillusol B. Key steps in this synthesis are an efficient Mitsunobu-iodination sequence and Sonogashira cross-coupling reaction (with a commercially available alkyne) followed by selective cyclic carbonate formation so as to generate the natural product.

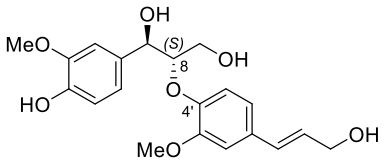


aspergillusol B

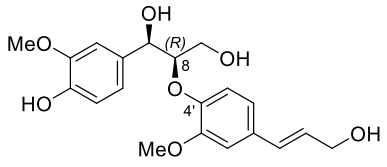
The final section of this thesis is comprised of **Publication 6**. This details work on the total synthesis of the four diastereomeric forms of the pro-angiogenic guaiacylglycerol 8-*O*-4′-coniferyl ethers (GGCE) shown below in an effort to establish the role stereochemistry plays on their capacities to act as pro-angiogenic agents.



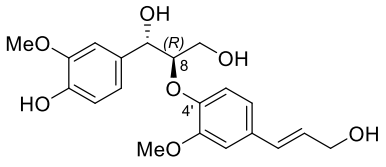
G



H



ent-**G**



ent-**H**

The syntheses feature an Evans/Seebach *syn*-aldol reaction utilising auxiliaries derived from either *L*-(+)- or *D*-(–)-valine. In the case of syntheses of the *anti*-compounds this was followed by a Mitsunobu inversion of the benzylic alcohol. The four diastereomers were assessed for their pro-angiogenic properties

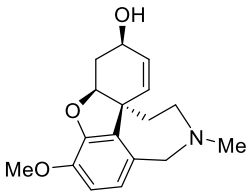
in a human microvascular endothelial cell tubule assay. Whilst they were all active, the compounds containing the 8*S*-ether linkage (*viz.* **G** and **H**) were the most potent.

The Appendices to this thesis are comprised of a series of reports arising from the single-crystal X-ray analyses of a number of key compounds synthesised by the author. These analyses and the derived reports are the result of work carried out by Dr Brett Schwartz, Dr Paul Carr and Dr Anthony Willis, the latter two being members of the Research School of Chemistry's Crystallographic Analysis Unit.

Thesis Overview

Publication 1: Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

(–)-Galanthamine is an alkaloid found in the bulbs of various *Amaryllidaceae* species including the Red Spider Lily (*Lycoris radiate*), the Caucasian snowdrop (*Galanthus woronowii)* and daffodils (*Narcissus poeticus*).[1–5] It is a centrally acting, selective and reversible competitive inhibitor of acetylcholine esterase (AChE).[3] The HBr salt (marketed as, *inter alia*, Nivalin, Razadyne and Reminyl) is currently used for the treatment of Alzheimer's Disease and is regarded as a frontline drug in the management of the growing dementia pandemic.[6,7] Its high cost of isolation and intriguing structure has resulted in it being an attractive target for total synthesis, as well as the focus of analoguing programs seeking systems displaying improved efficacy and/or reduced side-effects.[8–12]

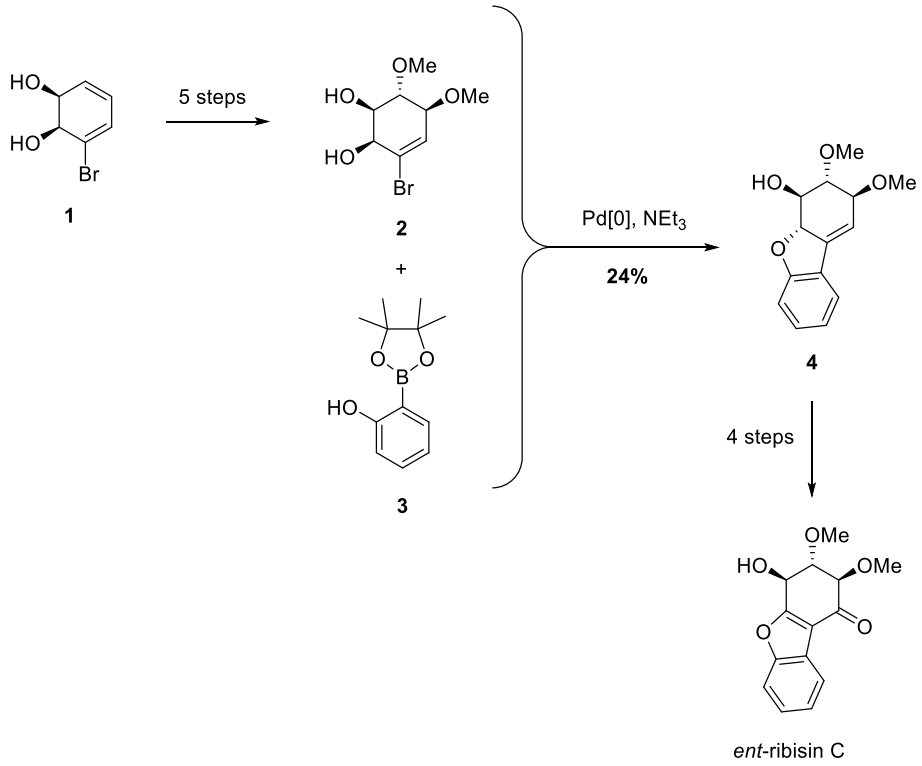


(–)-galanthamine

Publication 1 is an invited book chapter that highlights a number of important historical syntheses of galanthamine as well as new strategies being undertaken in the Banwell Group that are directed the towards the synthesis of this alkaloid and certain analogues.

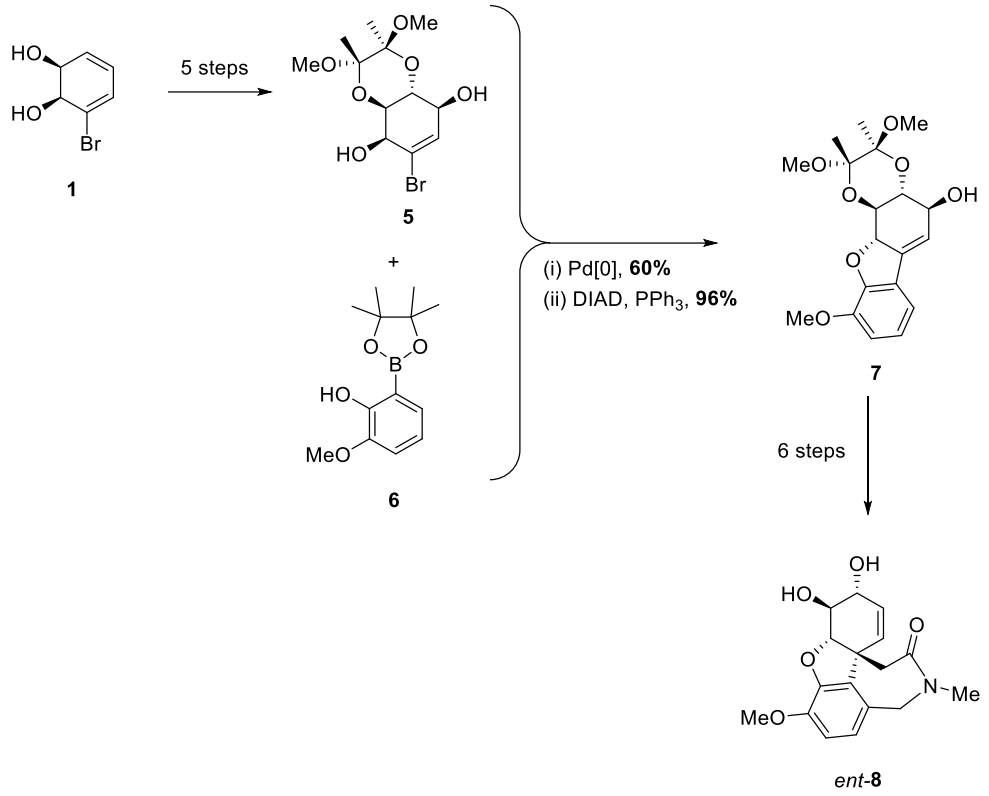
The chapter highlights how work on the synthesis of the structure assigned to the bioactive benzofuran natural product ribisin C (Scheme 1) inspired the author's own synthetic strategy towards the galanthamine framework. Specifically, when the functionalised bromoconduritol **2**, itself prepared from the *cis*-1,2-dihydrocatechol **1** (the focus of **Publication 2**), is subjected to Suzuki-Miyaura cross-coupling conditions with commercially available boronic acid ester **3** spontaneous cyclisation occurs to give 2,3-dihydrobenzofuran **4**, albeit in just 24% yield. This was converted, over four additional steps, into the structure assigned to

ribisin C. Analysis of the derived optical rotation and other spectral data revealed that this was actually the enantiomer of the natural product (*viz. ent*-ribisin C) and that, therefore, the structure of this end-product had been misassigned by the original workers.[13]



Scheme 1: Key steps used in the synthesis of *ent*-ribisin C

Inspired by this work, the author coupled compound **5**, itself derived from *cis*-1,2-dihydrocatechol **1**, with boronic acid ester **6** (Scheme 2) and was then able to effect a Mitsunobu cyclisation involving the product of this reaction to generate the ABC-ring containing 2,3-dihydrobenzofuran **7**. This last compound was then converted, over six additional steps, into the oxygenated derivative of (+)-galanthamine *ent*-**8**. This strategy is described in full in **Publication 3**.[14]



Scheme 2: Key steps used in constructing the ABC-ring system of (+)-galanthamine

Publication 2: Chemoenzymatic Pathways for the Synthesis of Biologically Active Natural Products

This review article details some of the ways in which enzymatically-derived *cis*-1,2-dihydrocatechols can be manipulated so as to generate a range of biologically active natural products. These metabolites are produced in homochiral form (>99.8% ee) through the enzymatic dihydroxylation of benzene derivatives using a genetically mutated strain of *E. coli* that overexpresses the enzyme toluene dioxygenase.[15] Figure 1 shows some of the key reactivities of *cis*-1,2-dihydrocatechols. Thus, the two centres of chirality can be used to direct the construction of other stereocenters associated with various complex molecules and additional functionality can be introduced *via* several means *e.g.* stereoselective electrophilic addition at the non-halogenated double bond,[16] cross-coupling to the alkenyl-halide residue,[17] or Diels-Alder reactions with the diene.[18]

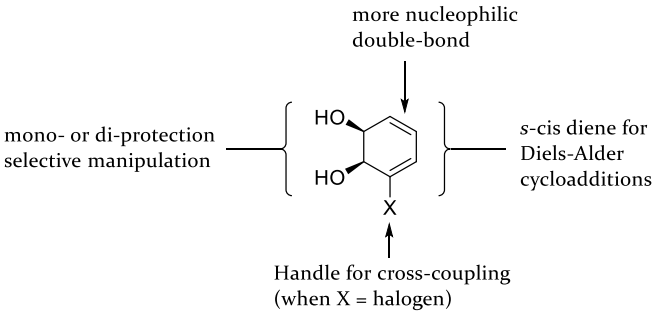


Figure 1: Key reactivities of *cis*-1,2-dihydrocatechols

The author's work on oxygenated analogues of (+)-galanthamine such as *ent*-**8** (Figure 2), which is itself the subject of **Publication 3**,[14] is highlighted as are syntheses of the ribisin class of natural product (including ribisin D),[19] (–)-platencin[18] and compound **10** which embodies the ABCDE-core of vindoline.[20]

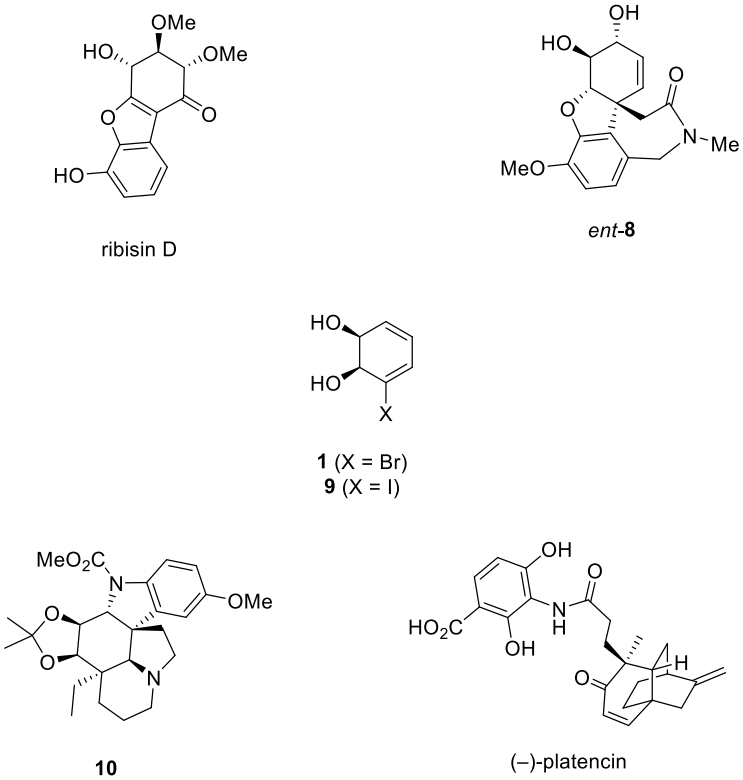
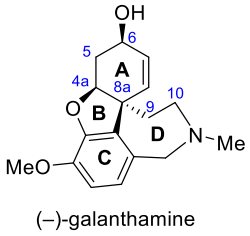


Figure 2: Examples of compounds prepared from the homochiral *cis*-1,2-dihydrocatechols **1** and **9**

Publication 3: The Synthesis of Certain Derivatives and Analogues of (–)- and (+)-Galanthamine and an Assessment of their Capacities to Inhibit Acetylcholine Esterase

Publication 3 details the author's investigations into syntheses of oxygenated analogues of the *Amaryllidaceae* alkaloid (–)-galanthamine and its enantiomer as well as an assessment of their AChE-inhibiting capacities.



(–)-galanthamine

Figure 3: The ABCD ring system of galanthamine and partial numbering scheme

Building upon the results highlighted in **Publications 1** and **2**, the author initially pursued the development of a total synthesis of (+)-galanthamine from *cis*-1,2-dihydrocatechol **1**. Intriguing results from docking studies (Table 1) of certain oxygenated derivatives such as compounds *ent*-**8** and *ent*-**11** (Figure 4) suggested that some of these would be potent inhibitors of AChE despite being related to the non-natural enantiomeric form of galanthamine.

Compound	Docking BE (kcal mol^{-1})
8	–8.9
ent- **8**	–9.6
11	–8.4
ent- **11**	–9.5
(–)-galanthamine	–10.2

Table 1: Docking energies of compounds **8**, **11** and their enantiomers

Given that the activity of galanthamine analogues oxygenated at the C5 position had not been previously explored and could, in principle, improve water solubility and provide a handle for conjugation,[10–12] the author pursued the synthesis of these derivatives and certain analogues in both enantiomeric series (Figure 4) in order that they could be subjected to biological evaluation.

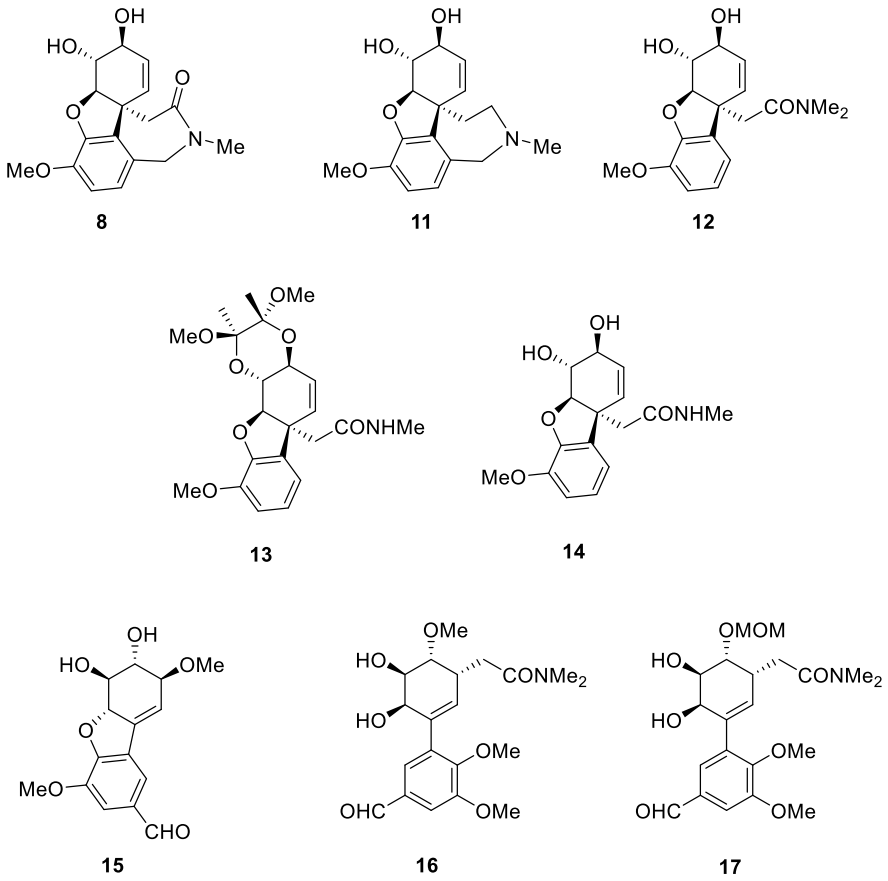
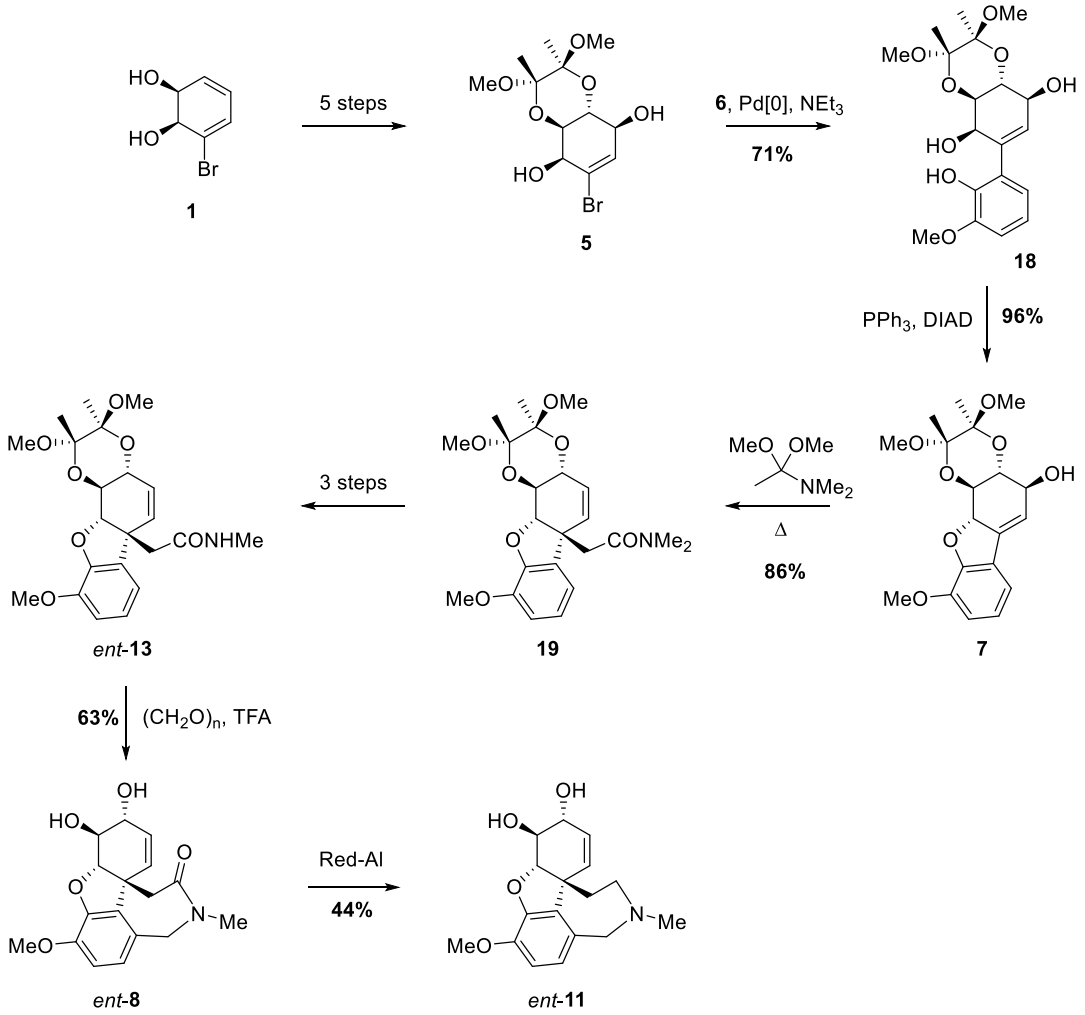


Figure 4: Compounds synthesised for biological evaluation in **Publication 3** (not shown: *ent*-**8**, *ent*-**11**, *ent*-**12**, *ent*-**13**, and *ent*-**14**)

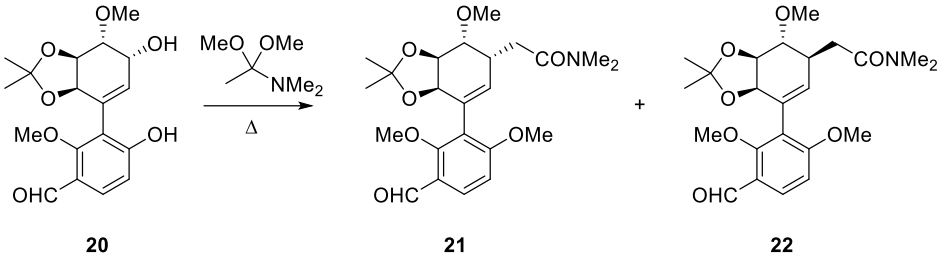
Compound **5** and its enantiomer are both accessible from *cis*-1,2-dihydrocatechol **1** (**Publications 1** and **2**) or *L*-(+)-tartaric acid (**Publication 4**), respectively. As shown in Scheme 3, compound **5** was engaged in a 3-step sequence involving Suzuki-Miyaura cross-coupling, intramolecular Mitsunobu and Eschenmoser-Claisen reactions to generate amide **19**. This sequence results in the rapid assembly of the ABC-ring system of galanthamine possessing the required stereochemistries at C6, C4a, C8a, and with an appropriate functional handle for constructing the D-ring. *N*,*N*-Dimethylamide **19** was then converted, over three steps, into the corresponding *N*-methylamide *ent*-**13** which, upon exposure to modified Pictet-Spengler conditions, cyclised to form lactam *ent*-**8**, thereby installing the D-ring. Reduction of compound *ent*-**8** with Red-Al® then delivered (+)-5-hydroxygalanthamine (*ent*-**11**). Compounds **12** and **14** (and their enantiomers) were prepared by hydrolysing the acetal unit of **19** and *ent*-**13**, respectively, under aqueous acidic conditions.



Scheme 3: Key steps in the synthesis of oxygenated galanthamine analogues from *cis*-1,2-dihydrocatechol **1**

Compounds **15** – **17** were prepared by Mr Ehab Taher using similar chemistries but where an aryl cross-coupling partner containing an aldehyde residue on the aromatic ring was employed.

Interestingly, although not without precedent,[21] when compound **20** was subjected to Eschenmoser-Claisen conditions the expected [3,3]-sigmatropic rearrangement did not take place. Rather, ionisation of the derived mixed acetal occurred and this was followed by its nucleophilic capture with 1-methoxy-*N,N*-dimethylethen-1-amine (a product of the thermal cracking of DMADMA) to give amide **21** and its C5 epimer **22** in a *ca.* 6:1 ratio (Scheme 4). The free phenolic residue was also methylated in the course of the reaction which is itself a well-known transformation observed upon thermolysis of compounds containing such functionalities with DMADMA or DMFDMA.[22]

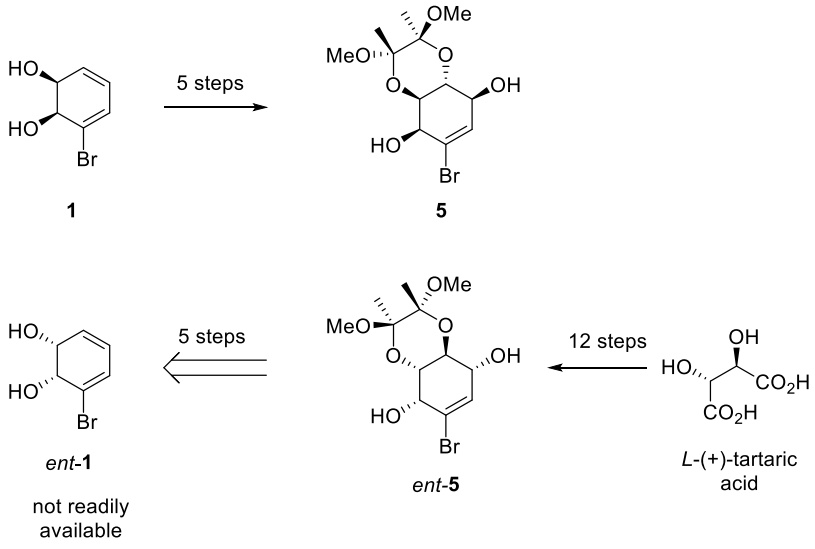


Scheme 4: 'Thwarted' Eschenmoser-Claisen rearrangement of allylic alcohol **20** leading to compounds **21** and **22**

Compounds **8**, **11** – **14** and their enantiomers as well as compounds **15** – **17** were evaluated for capacities to inhibit AChE and, in contrast to the predictions of the docking simulations outlined in Table 1, none bound strongly to this enzyme.

Publication 4: The Synthesis of Polyfunctionalized, Cyclohexene-Based Chirons from Tartaric Acid

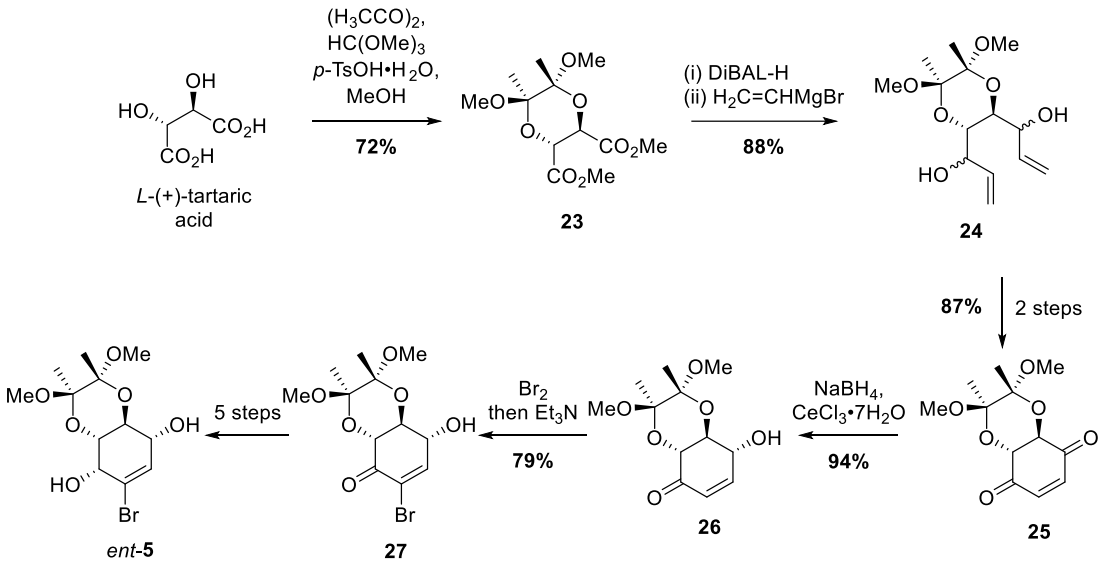
Despite the considerable utility of the *cis*-1,2-dihydrocatechols showcased in **Publication 2**, a major drawback is the inaccessibility of the enantiomers of these materials in homochiral form.[23] During our studies into the synthesis and biological evaluation of analogues of galanthamine (**Publication 3**), we required the enantiomer of compound **5** (Scheme 5).



Scheme 5: Synthesis of compounds **5** and *ent*-**5**

A 12 step synthesis of target *ent*-**5** is reported in **Publication 4** and is summarised in Scheme 6. Thus, *L*-(+)-tartaric acid was first converted into the 1,2-diacetal **23**

using an established a one-pot procedure.[24] Compound **23** was treated sequentially with two equivalents of DIBAL-H then seven equivalents of vinylmagnesium bromide, thereby generating *bis*-allylic alcohol **24**. This last compound was subjected to a ring closing metathesis then a 2-fold oxidation (using Dess-Martin periodinane) to afford the C_2-symmetric ene-dione **25**. Compound **25** itself was then reduced under modified Luche conditions at –78 °C to generate γ-hydroxyenone **26** as a single diastereomer and this last compound was brominated to afford α-bromocyclohexenone **27**. Compound **27** was elaborated to the target chiron *ent*-**5** over five additional steps that included reduction of the ketone moiety and subsequent Mitsunobu inversion of the undesired, pseudo-equatorial alcohol.



Scheme 6: Key steps employed in the synthesis of compound *ent*-**5** from *L*-(+)-tartaric acid

Figure 5 highlights some of the key features of the aforementioned homochiral cyclohexenones (*viz.* **26** and **27**). These are interesting chirons as both these and their enantiomers are available from cheap starting materials and contain various functional handles for further elaboration (*e.g.* cross-coupling to the alkenyl halide, Michael addition to the enone or Wittig olefination of the carbonyl). The 1,2-diacetal motif enforces a rigid conformation which aids stereocontrol[25] and the remaining stereogenic centres are easily manipulated through selective reductions and/or Mitsunobu chemistry. One such example of their utility in natural product synthesis is presented in **Publication 5**.

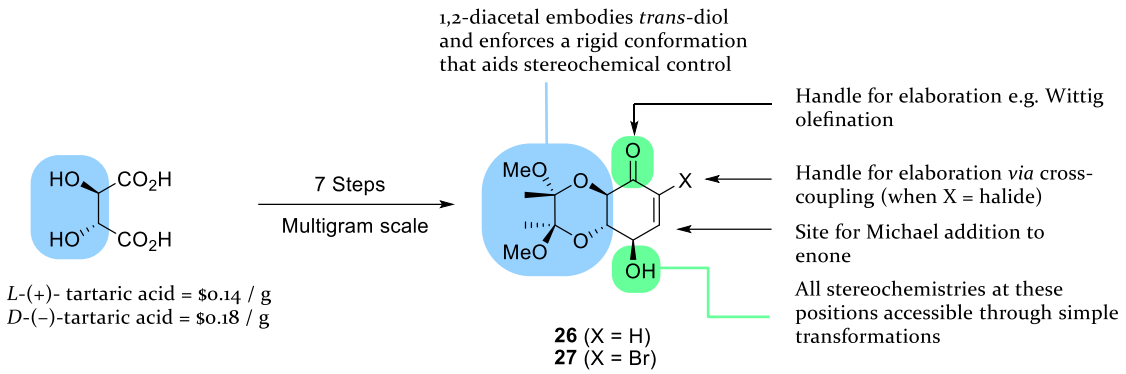


Figure 5: Key reactivities of tartaric acid-derived chirons

Publication 5: A Total Synthesis of the Cyclic Carbonate-Containing Natural Product Aspergillusol B from *D*-(–)-Tartaric Acid

In 2014 two novel cyclic carbonate-containing natural products were isolated, alongside the known compound (+)-asperpentyn,[26] from the culture broth of the fungus *Aspergillus* sp. PSURSPG185 found in soil samples collected from the Surat Thani Province in Thailand.[27] These were named aspergillusols A and B and assigned the structures shown in Figure 6.

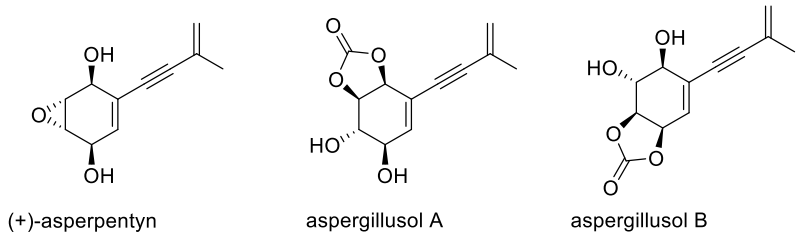
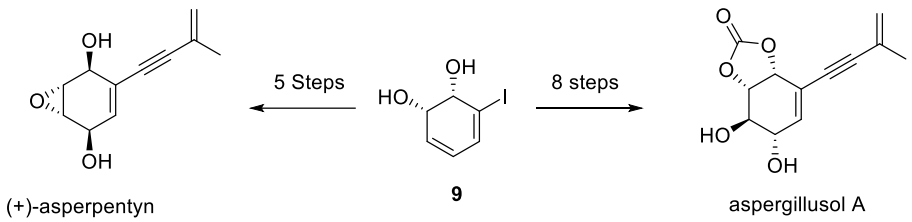


Figure 6: Structures assigned to the natural products (+)-asperpentyn, aspergillusol A and aspergillusol B

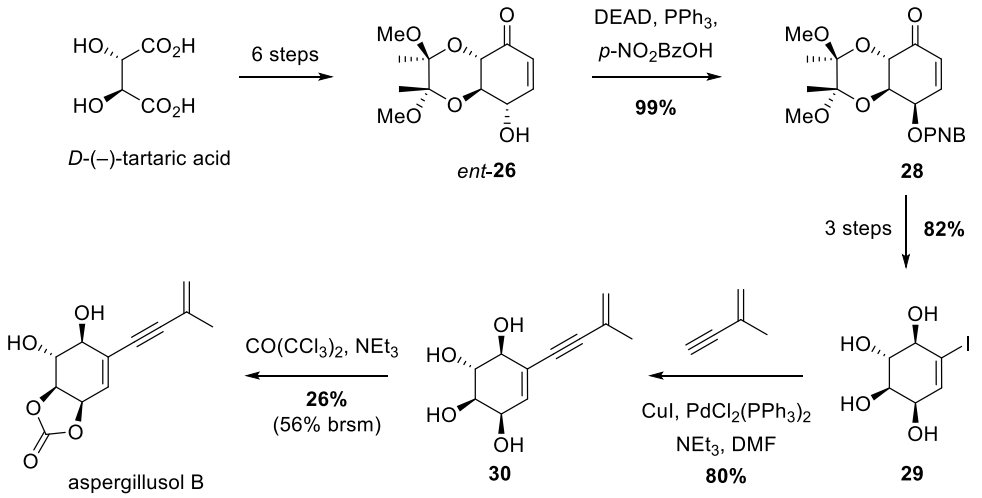
In 2015 Banwell and co-workers published total syntheses of (+)-asperpentyn and the enantiomer of aspergillusol A from *cis*-1,2-dihydrocatechol **9** in 5 and 8 steps, respectively (Scheme 7).[28]



Scheme 7: Syntheses of (+)-asperpentyn and aspergillusol A from enzymatically-derived chiron **9**

Cyclic carbonate-containing natural products are rare in nature[29,30] and it is likely that both aspergillusol A and B are formed *via* the *trans*-diaxial opening of the epoxide of (+)-asperpentyn with a carbonate nucleophile followed by a cyclisation event involving the adjacent *cis*-hydroxyl moiety.[31]

Publication 5 details a 12-step synthesis of the structure assigned to aspergillusol B from *D*-(–)-tartaric acid, thereby validating the structural assignment of Rukachaisirikul and co-workers.[27] Specifically (Scheme 8), *D*-(–)-tartaric acid is converted into the γ-hydroxyenone *ent*-**26** over 6 steps using the protocols outlined in **Publication 4**. Compound *ent*-**26** readily participated in a Mitsunobu reaction with *p*-nitrobenzoic acid to give ester **28** that was iodinated, reduced and deprotected to generate iodoconduritol **29**, the absolute stereochemistry of which was confirmed by single-crystal X-ray crystallography. This last compound engaged in Sonogashira reaction with the commercially available 2-methylbut-1-en-3-yne, efficiently installing the conjugated side-chain and generating tetraol **30**. Cyclic carbonate formation was then achieved by treating tetraol **30** with triphosgene in the presence of triethylamine and so producing aspergillusol B, albeit in rather modest yield. All the derived spectral data matched those of the naturally derived material but, as an optical rotation measurement was not obtained by Rukachaisirikul and co-workers the absolute stereochemistry of the natural product cannot be established at this time.



Scheme 8: Key steps associated with the author's synthesis of aspergillusol B from *D*-(–)-tartaric acid

Publication 6: Developing Neolignans as Pro-Angiogenic Agents: Stereoselective Total Syntheses and Preliminary Biological Evaluations of the Four Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers

Angiogenesis, the growth of new blood vessels, is central to the physiological processes of growth and repair in mammalian systems.[32] Whilst imbalances leading to excessive angiogenic activity can contribute to many ailments including inflammatory disorders, cancer and diabetes, insufficient angiogenesis can lead to problems with wound healing and organ repair.[33] Accordingly, compounds with pro-angiogenic activity are of interest for wound-healing as well as in the treatment of conditions such as acute muscle degeneration, diabetic retinopathy and the revascularization of ischemic tissues encountered in stroke victims and those suffering from cardiac disorders.[32–34]

In 2010, efforts by Djordjevic Group located within the ANU's Research School of Biology and the Parish Group in the John Curtin School of Medical Research (ANU) resulted in the isolation of two pro-angiogenic compounds from extracts of soybean *Glycine max*.[35] Although only small quantities were isolated, 2D NMR spectroscopic studies and mass spectral analyses led to the identification of these compounds as the two diastereoisomeric forms of guaiacylglycerol-8-*O*-4'-coniferyl ether (GGCE). Since the absolute stereochemistry of the active compounds could not be determined, the four possible structures that need to be considered are **31**, *ent*-**31**, **32** and *ent*-**32** (Figure 7).

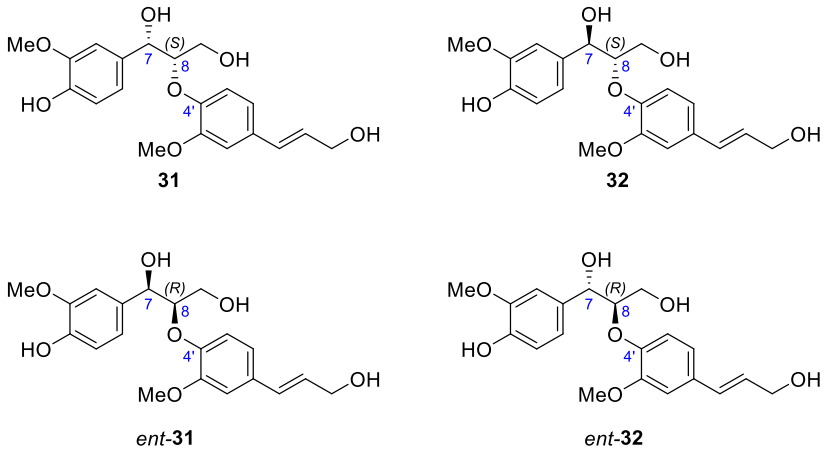
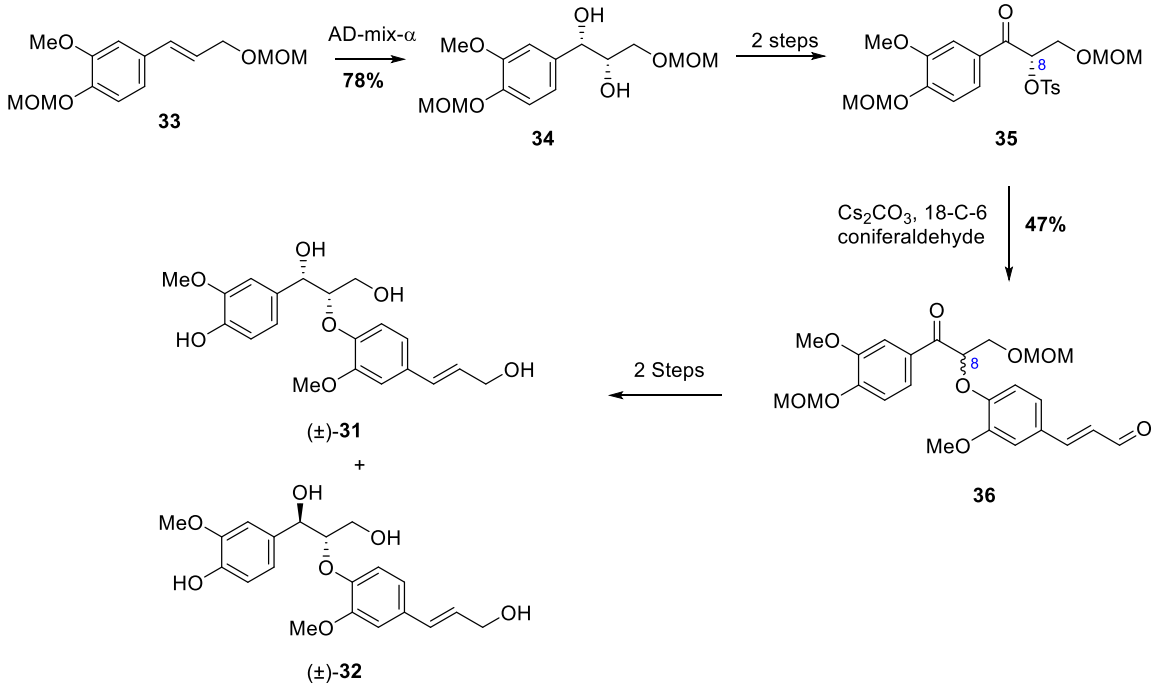


Figure 7: The four possible stereoisomeric forms of GGCE: **31**, *ent*-**31**, **32** and *ent*-**32** and partial numbering scheme

Publication 6 details the author's unambiguous total syntheses of compounds **31**, *ent*-**31**, **32** and *ent*-**32** and the evaluation of all four compounds as pro-angiogenic agents.

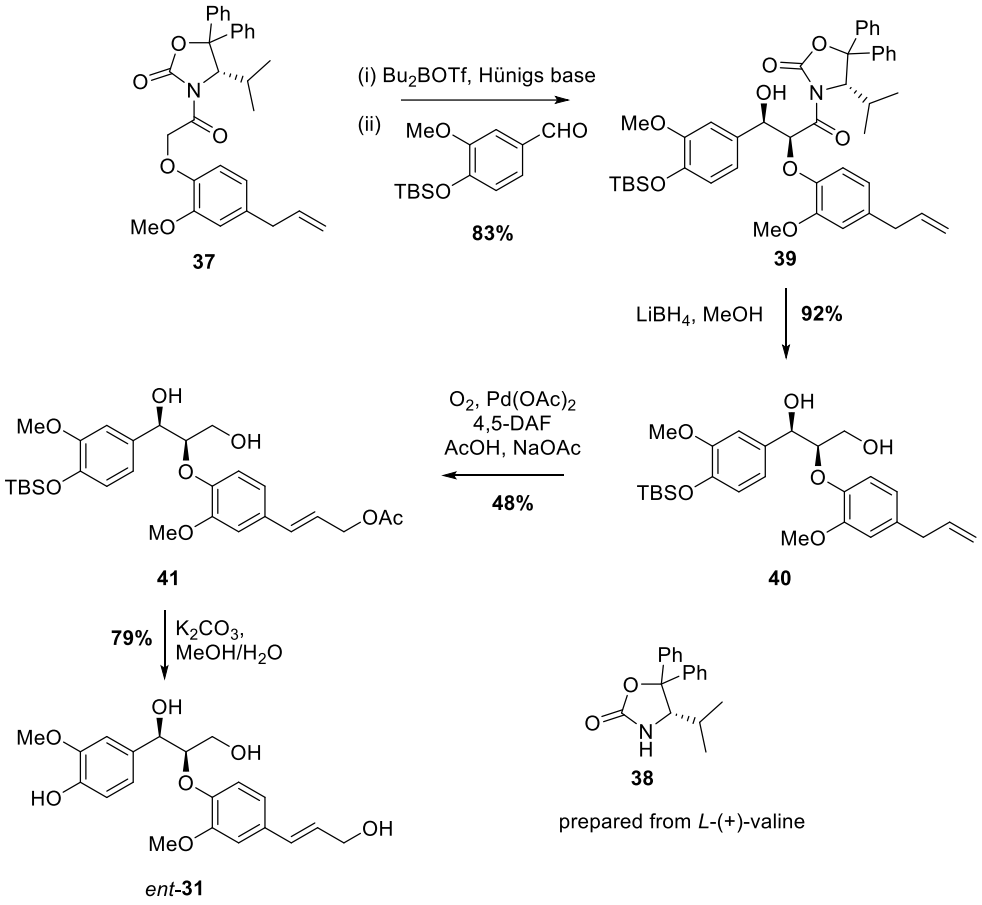
Initial attempts focused on the S_N2 displacement of tosylate **35** (Scheme 9), that was itself prepared from the known *bis*-MOM ether **33** through asymmetric dihydroxylation, selective oxidation of the benzylic alcohol and tosylation of the remaining free alcohol. After extensive experimentation, the reaction of compound **35** with the caesium salt of coniferaldehyde could be achieved in 47% yield but, unfortunately and not entirely surprisingly, the stereocenter at C8 underwent base-induced racemisation in the process. Despite this, syntheses of both compounds (±)-**31** and (±)-**32** were completed in two further steps which provided material for further biological evaluation and a means for determining the enantiomeric excesses of the subsequently generated enantiomerically enriched materials.



Scheme 9: First-generation syntheses of (±)-**31** and (±)-**32**

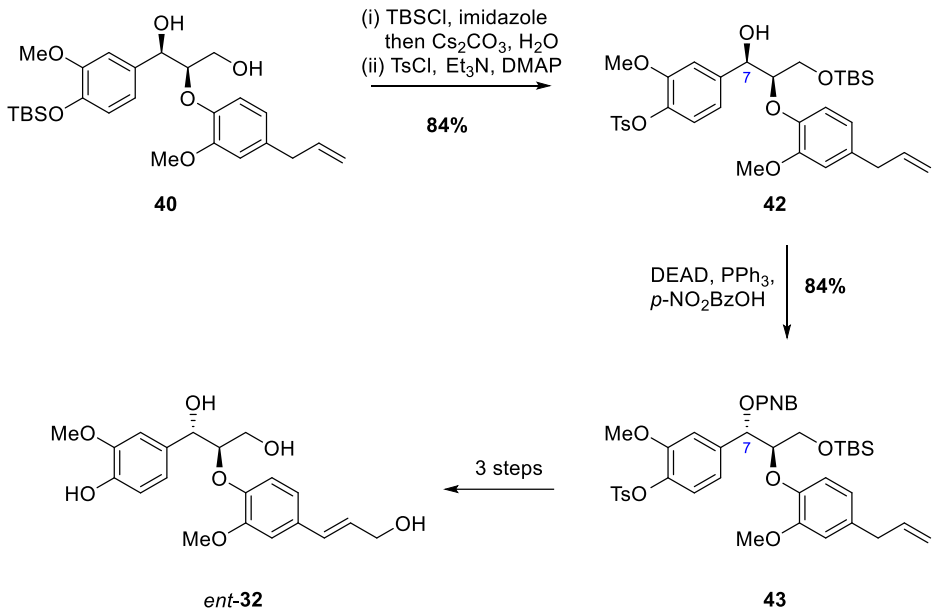
The second-generation syntheses of the target compounds achieved by the author are detailed in Scheme 10. This strategy utilises the valine-derived auxiliary **38** introduced by Seebach[36] and features an Evans' *syn*-aldol reaction of compound **37** with the TBS-ether of vanillin to establish the C7 and C8 stereochemistries

associated with the targets. After reductive cleavage of the auxiliary, the terminal alkene is engaged in an aerobic and palladium catalysed acetoxylation[37] to afford **41** and, after global deprotection under basic conditions, delivered compound *ent*-**31** in essentially homochiral (>99% ee) form (as judged by chiral HPLC analysis).



Scheme 10: Key steps used in the synthesis of compound *ent*-**31**

Subjection of alcohols **39** and **40** or certain related derivatives to Mitsunobu conditions in an effort to invert the stereochemistry at C7 and deliver the *anti*-compounds only led to complex mixtures of products. To attenuate the electron donating properties of the attached aryl oxygen that the author envisaged was facilitating ionisation of the activated benzylic alcohol intermediate,[38] silyl ether **40** was converted into tosylate **42** (Scheme 11). Gratifyingly, this ester engaged in a Mitsunobu reaction with *p*-nitrobenzoic acid with clean inversion of the stereochemistry at C7 and, after cleavage of the *p*-nitrobenzoate ester, acetoxylation and then global deprotection, compound *ent*-**32** was secured in essentially homochiral (>99% ee) form.



Scheme 11: Key steps in the synthesis of compound *ent*-**32**

Compounds **31** and **32** were prepared by analogous protocols using an auxiliary derived from *D*-(–)-valine. The absolute and relative stereochemistries of compounds **39** and *ent*-**39** were initially assigned based upon the well-established *syn*-selective outcomes of the Evans' boron aldol reaction.[36,39,40] Further support was later provided by the recent work of Nair and coworkers,[41] who prepared compound **32** using an *anti*-aldol protocol and undertook certain chemical correlation studies and a single-crystal X-ray analysis to establish the selectivities of their pivotal reaction.

Interestingly, all four compounds are active but exhibit different levels of pro-angiogenic activity, with the 8*S*- configured congeners **31** and **32** being the most potent. This is the first time that variations in stereochemistry have been shown to affect efficacy in small-molecule pro-angiogenic agents.

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Publication One

Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

Martin G. Banwell, Joshua Buckler, Colin J. Jackson, Ping Lan, Xinghua Ma, Eliška Matoušová and Jeremy Nugent

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Chapter Outline

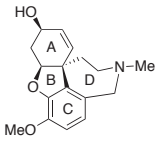
Abstract: The alkaloid (–)-galanthamine (**1**), a potent inhibitor of acetylcholine esterase (AChE), is used clinically for the symptomatic treatment of mild to moderate forms of Alzheimer's disease. The clinical demand for (–)-galanthamine together with the erosion of habitat of at least some of the source plants has created supply issues that have prompted numerous synthetic studies. Four distinct approaches for the assembly of the tetracyclic framework of compound **1** developed in the authors' laboratories are described here. Two of these exploit an enantiomerically pure metabolite produced through the whole-cell dihydroxylation of bromobenzene as a precursor to the A-ring of natural product **1**. The second of these rapidly provides enantiomerically pure compounds that molecular docking studies suggest should be strong inhibitors of AChE. A third synthesis of (–)-galanthamine involving the *de novo* assembly of the aromatic C-ring is also described, as is a failed radical cyclization-based approach.

Keywords: Alkaloid synthesis, Benzannulation, Bischler–Napieralski reaction, Bromoetherification, *cis*-1,2-dihydrocatechol, Eschenmoser–Claisen rearrangement, Galanthamine, Intramolecular Alder-ene reaction, Mitsunobu reaction, Pictet–Spengler reaction, Radical cyclization, Ribisins, Smiles rearrangement, Suzuki–Miyaura cross-coupling reaction

1. Introduction

The alkaloid (–)-galanthamine (a.k.a. galantamine, **1**) has been obtained from a variety of plant sources including Caucasian snowdrops (*Galanthus woronowii*), the summer snowflake (*Leucojum aestivum*), the wild daffodil *Narcissus pseudonarcissus* and the Red Spider Lily (*Lycoris radia*).[1] Various mythologies suggest that crude extracts of such plants have been used for millennia to treat a range of ailments but it was only in 1950 that a rather more specific report seems to have emerged on the utility of these materials. In particular, at this time a Bulgarian pharmacologist was supposed to have noted that rural populations in certain parts of Eastern Europe would rub snowdrops on their foreheads to alleviate headaches.[1a,d] Within a few years, and perhaps prompted in part by these observations, Russian researchers extracted (–)-galanthamine from *Galanthus woronowii* and were using it as a treatment for poliomyelitis, and seemingly to considerable effect.[1a,d,2] At about the same time it was also being employed in anaesthesiology as a curare reversal agent, as a treatment for myasthenia (an autoimmune or congenital neuromuscular disease) and myopathy (a muscular disease resulting in weakness) as well as for sensory and motor dysfunctions associated with CNS disorders.[1,3] However, it was the recognition that this alkaloid is a selective, competitive and reversible inhibitor of the enzyme acetylcholinesterase (AChE)[1] that can cross the blood-brain barrier that propelled it into the limelight and thence into the clinic (in the US, Europe and Japan) as an agent for the symptomatic treatment of mild to moderate vascular dementia and Alzheimer's disease.[1,4] It has also been shown to act at the nicotinic acetylcholine receptor as an allosteric potentiation ligand with the result that it triggers increased release of dopamine, serotonin, γ-aminobutyric acid, norepinephrine and related neurotransmitters.[1,5] The HBr salt of compound **1** (marketed as, *inter alia*, Nivalin, Razadyne and Reminyl) is now considered a frontline drug in helping combat the

emerging dementia pandemic. Various recent clinical case studies stand as testimony to its utility in this regard.[6]



1
[(–)-galanthamine]

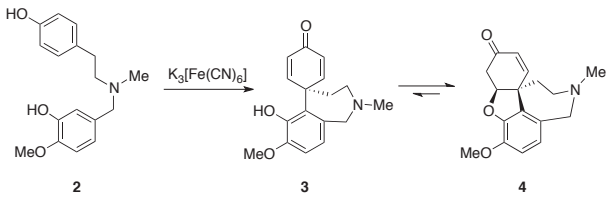
The clinical demand for (–)-galanthamine together with the erosion of habitat of at least some of the source plants has created supply issues.[1b,7] As a result new means of production of the alkaloid are being sought with *in vitro* cultivation and pathway optimization techniques[7] (in which the biosynthetic pathway[8] is "tweaked") being prominent amongst these. To date no industrially applicable (cost-effective) chemical synthesis of compound **1** has emerged[9] that addresses this supply problem although a pilot scale and biomimetic production process has been reported.[10]

As is almost invariably the case with natural-product based drug development programs, significant effort has been directed towards the identification of analogues of (–)-galanthamine with improved efficacy and/or reduced side effects (compound **1** causes, *inter alia*, gastrointestinal problems). Such studies, which are now assisted by high-resolution X-ray structures of AChE/**1** and related complexes,[11] have involved traditional medicinal chemistry,[1b,12] sophisticated QSAR analyses,[13] "biomimetic diversity-oriented synthesis"[14] and related techniques exploiting various multicomponent reactions.[15] In parallel, natural products chemists continue to screen extracts from various biological sources for new metabolites (notably alkaloids) that display AChE inhibitory properties.[16]

The circumstances described in the preceding paragraphs when considered together with the intriguing molecular architecture of (–)-galanthamine have, unsurprisingly, prompted a significant number of research groups to undertake total synthesis studies. In order to put our own group's contributions to this area into an appropriate context, some commentary on other studies of the synthesis of galanthamine is warranted. This is provided in the following section.

2. Studies on the Synthesis of Galanthamine – A Potted History

In 1960 Barton and Kirby reported[17] the first synthesis of (±)-galanthamine and thereby confirming its structure. This involved a biomimetic but low yielding (1.4%) intramolecular phenolic oxidative coupling of compound **2** (Scheme 1) to generate the spiro-fused dienone **3** that engages in a reversible intramolecular hetero-Michael addition reaction to give narwedine (**4**) that was itself converted into (±)-galanthamine on exposure to $LiAlH_4$.[17]

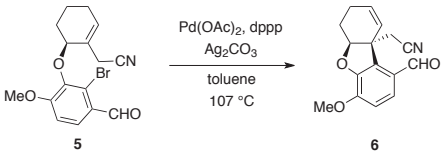


SCHEME 1: The Barton–Kirby Biomimetic Synthesis of Narwedine (**4**).

Various improvements to this process have been achieved by using, *inter alia*, slightly different substrates and/or other oxidants (notably hypervalent iodine compounds) in the pivotal coupling step.[18] An asymmetric variant of this process has been introduced[19] although this is not essential because racemic narwedine is resolved, through crystallization, into its (–)-form in the presence 1% (+)-galanthamine (*viz. ent*-**1**).[20,21] Reduction of (–)-narwedine with L-Selectride

then affords (–)-galanthamine in 99% yield.[20,22] In 2009 Magnus and co-workers reported[23] a somewhat related synthesis of compound **1** in which an intramolecular phenol alkylation was applied to a biphenyl-containing substrate and thus affording a spiro-dienone that could be converted, over three simple and efficient steps, into (±)-narwedine (**4**).

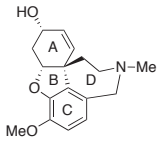
The ABC-ring system of (–)-galanthamine has also been constructed using intramolecular Heck reactions with a particularly notable and early example being described by Trost and Toste.[24] Specifically, they showed (Scheme 2) that on exposure to 15 mol % $Pd(OAc)_2$, 15 mol % of the ligand diphenylphosphinopropane (dppp) and 3 mole equiavlents of Ag_2CO_3 the allylic ether **5**, itself the product of an asymmetric allylic alkylation (AAA) reaction, was converted into compound **6** (91%). This was then carried forward over a further four steps into (–)-galanthamine.



SCHEME 2: The Pivotal Intramolecular Heck Reaction Associated with the Trost/Toste Synthesis of (–)-Galanthamine (**1**).

Several variations on this type of approach have been reported[25] as have other ingenious schemes[26,27] leading to compound **1**, the corresponding racemate or its optical antipode (*viz. ent*-**1**). Of particular relevance to the present discussion is Chida's synthesis of (+)-galanthamine from *D*-glucose using a combination of type-II Ferrier and Claisen rearrangement protocols. Details of this elegant work have recently been described in a personal account[27b] and are not,

therefore, presented here. It is, however, appropriate to note that, like Chida's, a significant fraction of our research effort has been devoted to devising means by which certain chiral-pool derived starting materials can be elaborated to a range of biologically active natural products. The chirons we have chosen to investigate for this purpose, including in developing certain of the various approaches to galanthamine reported here, are the *cis*-dihydrocatechols of the general form **7**.[28] Many of these compounds are available in kilogram quantities and essentially enantiomerically pure form through the whole-cell biotransformation of the corresponding aromatic, e.g. bromobenzene.



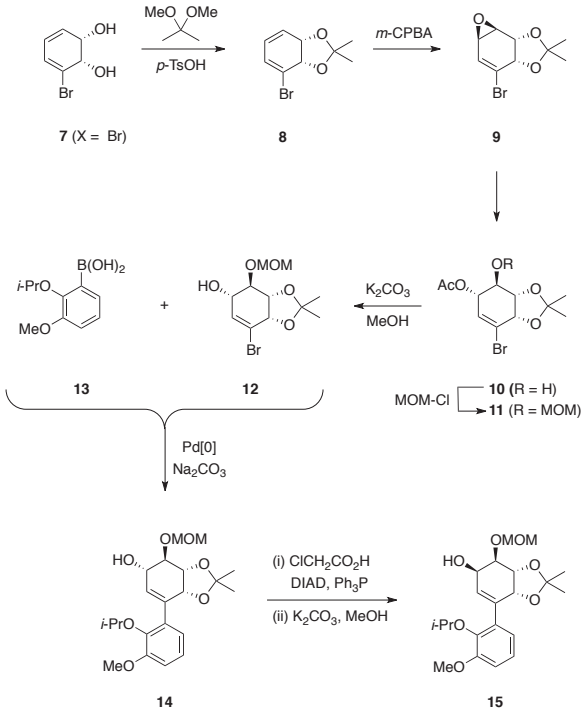
ent-**1**
[(+)-galanthamine]

7
(X = Me, Cl, Br, I...)

3. A First-Generation Chemoenzymatic Synthesis of (+)-Galanthamine

Our initial foray into the area of galanthamine synthesis was motivated a desire to see if we could parlay our knowledge[28e] of the chemistry of *cis*-1,2-dihydrocatechols into a reaction sequence that would allow for the elaboration of compound **7** (X = Br) into the A-ring of (+)-galanthamine (*ent*-**1**). This non-natural form of the alkaloid was targeted in the first instance simply because this seemed to "map" more appropriately onto the chirality of the proposed starting material. That having been said, the compound *ent*-**7** (X = Br) is also available[28e] (although it is not quite as accessible as its enantiomer) and so any success achieved in gaining access to (+)-galanthamine from *cis*-1,2-dihydrocatechol **7** (X = Br) automatically "translates" into a means for obtaining the natural product, *viz*. compound **1**.

The opening steps of our ultimately successful synthesis of (+)-galanthamine (*ent*-**1**)[29] from metabolite **7** (X = Br) are shown in Scheme 3 and involved the initial conversion of the latter into the corresponding and well known acetonide **8**.

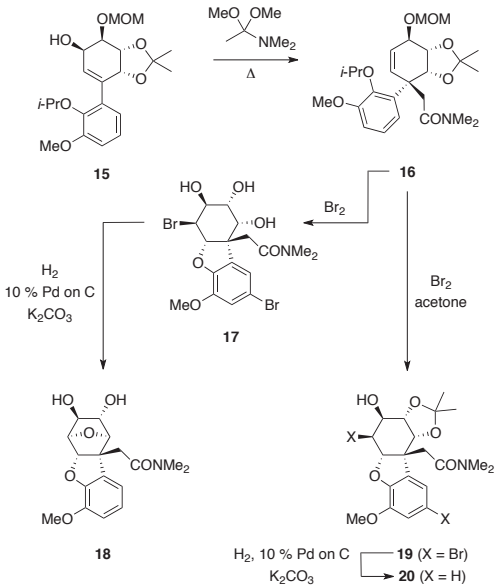


SCHEME 3: Opening Stages of a First-Generation Chemoenzymatic Synthesis of (+)-Galanthamine (*ent*-**1**).

This step provides a trap for young players in that if not carried out carefully an almost explosive acid-catalyzed dehydration and re-aromatization reaction of the substrate and/or product occurs. Regio- and stereo-controlled epoxidation at the β-face of the non-halogenated double bond within compound **8** is readily effected using *m*-chloroperbenzoic acid (*m*-CPBA)

and the epoxide **9** (90% over two steps) so-formed is then engaged in a completely selective and mineral acid catalyzed ring opening reaction with acetic acid serving as the nucleophile so as to generate alcohol **10** (81%). This is immediately protected as the corresponding MOM-ether **11** (91%) (forcing conditions required) and the associated acetate group hydrolyzed to the corresponding alcohol **12** (95%). This cyclohexenyl bromide participated in a Suzuki–Miyaura cross-coupling reaction with the readily obtained boronic acid **13** to afford the arylated cyclohexene **14** (98%). The single free hydroxyl group embedded within this last compound was engaged in a Mitsunobu reaction using α-chloroacetic acid as the nucleophile and the product ester immediately hydrolyzed using potassium carbonate in methanol to give the epimeric compound **15** (93% over two steps).

The next and particularly crucial phase of the synthesis was the construction of the quaternary carbon center associated with galanthamine as well as the formation of the furan or B ring. While it took sometime to establish the right sequence of reactions to realize such an outcome, this was eventually achieved in just three steps (Scheme 4), the first being the engagement of the allylic alcohol moiety within compound **15** in an Eschenmoser–Claisen (EC) rearrangement by treating it with the dimethyl acetal of *N*,*N*-dimethylacetamide in refluxing toluene for seven days. The amide **16** (89%) so-formed now embodies the requisite quaternary carbon center with the illustrated configuration and thus dictating that it is the (+)-form of galanthamine that will ultimately be obtained by this route.

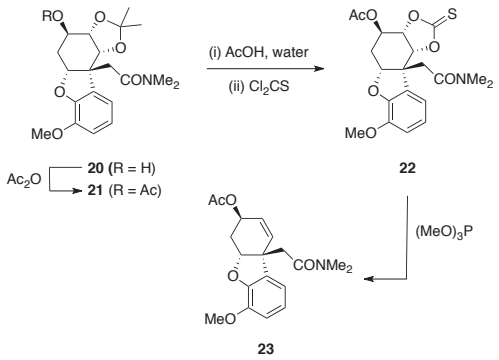


SCHEME 4: Establishing the Quaternary Carbon Center and B-ring of (+)-Galanthamine

Notably, the epimer of and precursor to allylic alcohol **15**, namely compound **14**, also engages in an analogous but even more sluggish EC rearrangement and thereby delivering the epimer of compound **16**. In principle, this epimer could serve as a precursor to (–)-galanthamine. Treatment of compound **16** with molecular bromine in toluene resulted in three distinct events: (i) cleavage of both the isopropyl aryl ether and acetonide residues; (ii) a bromo-etherification reaction (to form the desired B-ring) and, (iii), a S_EAr reaction at the electron-rich arene moiety. As a result compound **17** (69%) was obtained but on attempting to reductively debrominate it through exposure to dihydrogen in the presence of 10% Pd on C and potassium carbonate then, *inter alia*, a transannular etherification reaction took place and so producing the undesired 7-oxabicyclo[2.2.1]heptane **18** (67%). However, through the simple expedient of treating substrate **15** with molecular bromine in the presence of a mixture of toluene and acetone

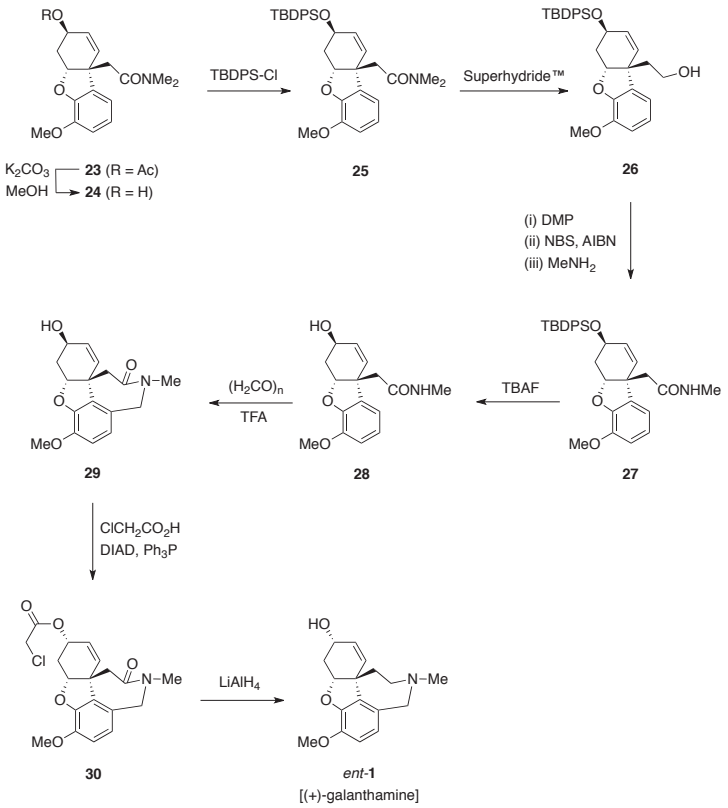
then the acetonide residue could be retained while the isopropyl aryl ether was still cleaved and with the product phenol participating, once again, in a bromoetherification reaction involving the pendant double bond of the A-ring and so affording the dibromide **19** (93%). Reductive debromination of this last compound now proceeded as desired to afford compound **20** (68%) that embodies the desired ABC-ring substructure of target *ent*-**1**.

The next phase of what was rapidly becoming a distinctly lengthy synthesis was the replacement of the now "longstanding" acetonide residue within the developing A-ring by a double bond residue. As is almost inevitable, a Corey–Winter olefination protocol was employed for this purpose. Thus, the free hydroxyl group within the A-ring of compound **20** was protected (Scheme 5) as the corresponding acetate **21** (90%) and the acetonide residue within the latter was cleaved and the diol so-formed immediately converted into the corresponding cyclic thiocarbonate, **22** (99%), by treating it with thiophosgene in the presence of 4-(*N*,*N*-diemthylamino)pyridine (DMAP). Exposure of compound **22** to a large excess of trimethylphosphite in toluene then gave the desired olefin **23** (72%).



SCHEME 5: Installing the A-Ring Double Bond

The heroic end-game "played" by Dr Xinghua Ma in completing our first generation chemoenzymatic synthesis of (+)-galanthamine is outlined in Scheme 6 and involved, as the first steps, subjecting compound **23** to an initial cleavage of the A-ring acetate group and reprotection of the resulting alcohol **24** (95%) as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether **25** (95%). This was a necessary prelude to using Superhydride™ to reduce the associated amide residue to the corresponding 2°-alcohol and thus forming compound **26** (95%). A two-pot reaction sequence followed wherein the alcohol **26** was oxidized to the corresponding aldehyde (using the Dess–Martin periodinane – DMP) that was itself subjected to a free-radical bromination with the product acyl bromide then being trapped *in situ* by added methylamine. This afforded the mono-*N*-methylated amide analogue **27** (76%) of precursor **25**. Desilylation of compound **27** using tetra-*n*-butylammonium fluoride (TBAF) and engagement of the product **28** (85%) in a Pictet–Spengler reaction using paraformaldehyde in trifluoroacetic acid (TFA) resulted in closure of the D-ring and, thereby, formation of the lactam **29** (88%). The final two steps were devoted to establishing the correct stereochemistry of the A-ring hydroxyl group and this required engagement of compound **29** in a Mitsunobu reaction using α-chloroacetic acid as the nucleophile and then subjecting the product ester/lactam **30** (93%) to a "global" reduction using $LiAlH_4$ and so providing (+)-galanthamine (*ent*-**1**) (85%), the high-field NMR spectral data for which matched those recorded on an authentic sample of its enantiomer.



SCHEME 6: The End-Game Associated with the First-Generation Chemoenzymatic Synthesis of Galanthamine (*ent*-**1**).

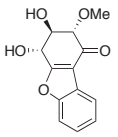
Clearly there are many deficiencies associated with this synthesis. While it could be certainly be tweaked in various ways (perhaps most notably by "fiddling" with protecting group regimes), the more important aspects of this work were the lessons learnt *en route*. In particular, the EC rearrangement reaction "shone through" as an almost uniquely effective means for establishing the quaternary carbon center of (+)-galanthamine from a precursor 2-cyclohexen-1-ol. This lesson came to the fore in our next and almost accidentally discovered second-

generation chemoenzymatic approach to galanthamine. How all this unfolded is described in the following section.

4. Total Syntheses of Members of the Ribisin Class of Neurologically Active Natural Product Inspire a Second-Generation Chemoenzymatic Approach to (+)-Galanthamine

4.1 The Ribisins

In 2012 Fukuyama and co-workers reported[30] the isolation of four new and structurally novel natural products from the fungus *Phellinus ribis*, the fruiting bodies of which are employed in traditional Chinese medicine for enhancing immunity and treating gastrointestinal cancer. On the basis of various spectroscopic analyses the benzofuran structures **31**, **32**, **33** and **34** were assigned to these compounds that were named ribisins A–D, respectively.



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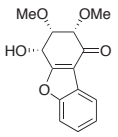

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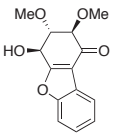

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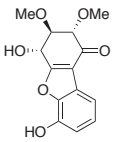

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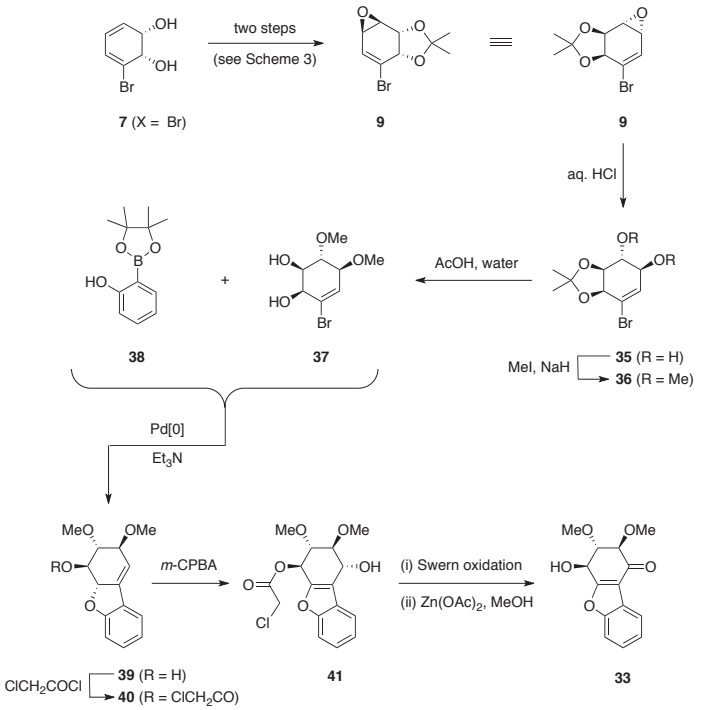
It was also noted that at 1 to 30 μM concentrations these natural products promote neurite outgrowth in NGF-mediated PC12 cells and could thus represent new leads for developing drugs to treat various neurodegenerative diseases.

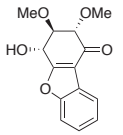
The resemblance of the polyoxygenated rings of the ribisins to the *cis*-1,2-dihydrocatechols of the general form **7** immediately struck us and prompted consideration of methods by which we could effect the necessary conversion. Our initial efforts[31] were focused on synthesizing the structure, **33**, assigned to ribisin C since this was the most active of the four compounds in the PC12-based assay. The reaction sequence used to obtain this compound is shown in Scheme 7.



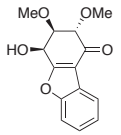
SCHEME 7: A Chemoenzymatic Synthesis of the Structure **33**, Assigned to Ribisin C

As with our first-generation synthesis of (+)-galanthamine, the reaction sequence leading to compound **33** started with the same *cis*-1,2-dihydrocatechol and this was first converted into the previously described epoxide **9**. Opening of this with aqueous HCl then provided the expected *trans*-diol **35** (63%) that was subjected to a two-fold methylation reaction and so generating compound **36** (90%) embodying the two *trans*-related methoxy residues associated with target compound **33**. Hydrolysis of the acetonide residue within bis-*O*-methyl ether **36** then afforded the *cis*-diol **37** (90%) that participated in a Suzuki–Miyaura cross-coupling reaction with the commercially available *o*-hydroxyphenyl boronic acid ester **38**. As a result the cyclohexannulated benzofuran-type system **39** (24%) was obtained and this presumably arises from the spontaneous cycloetherification of the initially formed cross-coupling product. In anticipation of introducing a hydroxyl group as a precursor to the required ketone carbonyl, alcohol **39** was protected as the corresponding α-chloroacetate **40** that we knew, from previous experience, could be removed under exceptionally mild conditions. Treatment of cyclohexene **40** with *m*-CPBA afforded the benzofuran **41** (49% from **39**) that presumably arises through rearrangement of the initially formed epoxide, a process driven by rupture of the strained three-membered ring and accompanying formation of the aromatic heterocycle associated with the observed product. Swern of oxidation of the alcohol residue within compound **41** and cleavage of the α-chloroacetate moiety within the product ketone using zinc acetate in methanol then gave target **33** (47% from **41**), the structure and relative stereochemistry of which were established by single-crystal X-ray analysis. While the ^{1}H and ^{13}C NMR data acquired on compound **33** matched those reported for ribisin C, the similar magnitudes but opposite signs associated with the specific rotations of these two materials clearly indicated that the absolute stereochemistry of the natural product had been assigned incorrectly.

As a result of the outcome just described, and because of a desire to acquire biologically active materials for testing for their neurite outgrowth promoting properties, we rapidly established[31] a reaction sequence that enabled the synthesis of compound *ent*-**33** and thus determining that this is the true structure of ribisin C. Once again, the staring material used for this purpose was the *cis*-1,2-dihydrocatechol **7** (X = Br). Using related chemistries we also prepared compounds **31**, **32** and **34** and thereby establishing[32] that the first and third of these do indeed represent the structures of ribisins A and D. Such work also enabled us to identify the true constitution of ribisin B as being represented by structure **42** and not **32**. The substantial collection of compounds produced during the course of our work on the synthesis of the ribisins has been submitted for testing in a range of relevant assays.



ent-**33**



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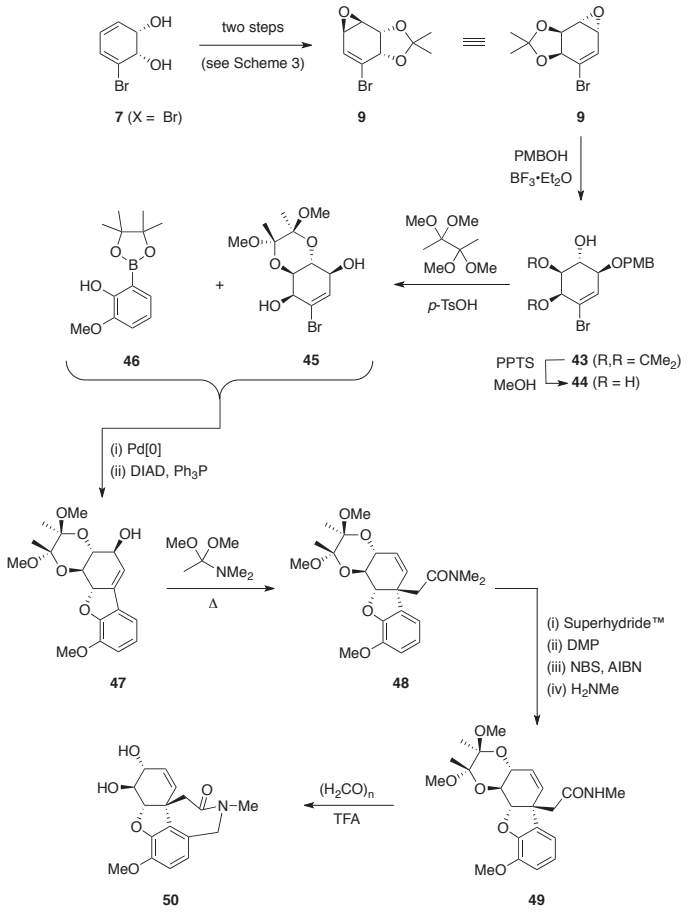
4.2 A Second-Generation Chemoenzymatic Approach to the Synthesis of (+)-Galanthamine

Rather belatedly, it occurred to us that our synthetic work on the ribisins might provide a means of readily assembling the ABC-ring system associated with galanthamine and perhaps even the alkaloid itself. There certainly appears to be some validity to this proposition as evidenced by the completion of the reaction sequence shown in Scheme 8.[33]



SCHEME 8: A Second-Generation Chemoenzymatic Approach to (+)-Galanthamine (*ent*-**1**).

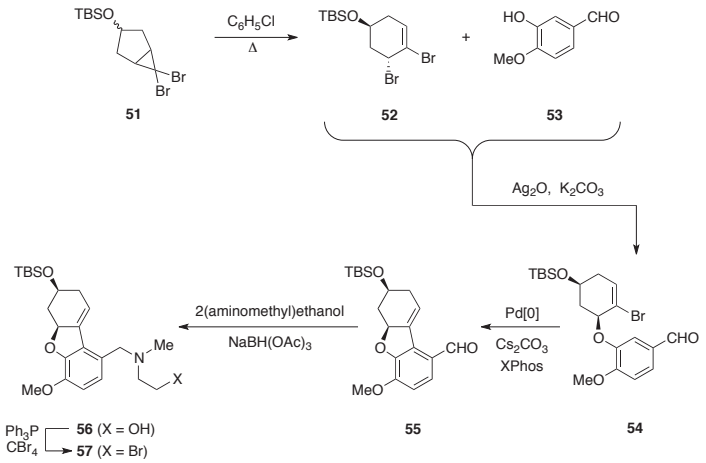
Once again, the reaction sequence starts with the *cis*-1,2-dihydrocatechol derived from the whole-cell biotransformation of bromobenzene, *viz*. compound **7** (X = Br), but the derived epoxide **9** is now opened with *p*-methoxybenzyl alcohol (PMBOH) in the presence of BF_3•Et_2O to give the tri-protected bromoconduritol **43** that upon exposure to pyridinium *p*-toluenesulfonate (PPTS) in methanol affords its mono-protected counterpart **44** (70% from **9**). Reaction of this last compound with 2,2,3,3-tetramethoxybutane in the presence of catalytic quantities of *p*-TsOH then provided the Ley-type[34] bis-ketal **45** (86%) in which, by virtue of the

operation of the anomeric effect, completely selective protection of the vicinally-related and *trans*-oriented hydroxyl groups within substrate **44** had occurred together with cleavage of the PMB ether moiety. Suzuki–Miyaura cross coupling of compound **45** with the arylboronic acid ester **46**, a compound that is readily obtained in a one-pot process from *o*-methoxyphenol using a protocol described by Hartwig,[35] afforded the anticipated product (60%) that readily engaged in an intramolecular Mitsunobu reaction to give the targeted ABC-ring containing product **47** (96%). This last compound might have been expected to be vulnerable to double-bond migration and thereby forming the isomeric and fully aromatic benzofuran. Nevertheless, and gratifyingly, it engaged in a very efficient and remarkably facile EC rearrangement reaction on being heated with dimethyl acetal of *N*,*N*-dimethylacetamide and so affording compound **48** in 86% yield. A distinctly cumbersome four-step sequence closely related to that deployed in the end-game associated with our first generation galanthamine synthesis (Scheme 6) was then used to convert this *N*,*N*-dimethylacetamide derivative into its mono-methylated counterpart **49** (73% over four steps). This last compound participated in a Pictet–Spengler reaction on treatment with paraformaldehyde in TFA, a process that was accompanied by cleavage of the associated bis-ketal moiety, and so forming the galanthamine analogue **50** (47%).

Efforts are now underway to effect the conversion of lactam **50** into (+)-galanthamine (*ent*-**1**). Interestingly, molecular docking studies similar to those reported previously[36] suggest this compound (*viz.* **50**) should bind at the active site of AChE with similar affinity to (–)-galanthamine itself. This is because the cyclohexene C-ring (of **50**) is oriented almost identically to its counterpart in (–)-galanthamine and so maintaining an architecture complementary to that of the active site of AChE and whereby it stacks against the indole ring of Trp84. Whether or not this rather tantalizing prediction is indeed correct remains to be tested experimentally.

5. An Abortive, Radical-Based Approach to (±)-Galanthamine

During the course of studies focused on the synthesis of certain crinine alkaloids we conceived of another and now exceptionally concise route to the ABC-ring substructure of galanthamine and hoped that the product so-formed would be capable of elaboration in such a way that the nitrogen-containing D-ring of the alkaloid could be annulated to it. The steps associated with the first stage of this study[36] are shown in Scheme 9 and involved a thermally-induced electrocyclic ring-opening of the readily available C3-oxygenated 6,6-dibromocyclopropane **51** and engagement of the product dibromocyclohexene **52** in an S_N2 reaction with phenol **53** to give the allyl aryl ether **54** (*ca*. 80% from **51**). This last compound

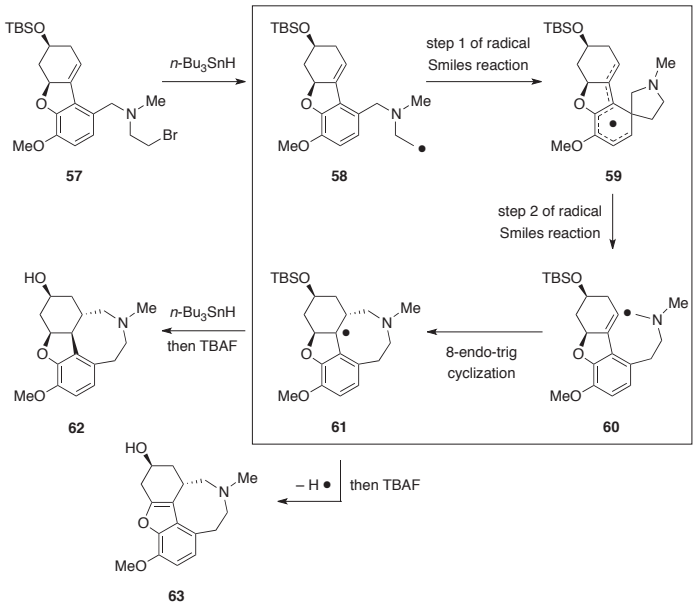


SCHEME 9: A Concise, Cyclopropane-Based Route to the ABC-Ring Substructure of Galanthamine

then participated in a Pd-catalyzed and intramolecular arylation reaction under conditions developed by Willis *et al.*[37] to give the tetrahydrodibenzo[*b*,*d*]furan **55** (ca. 65%). Reductive amination of compound **55** with *N*-methyl-2-aminoethanol in the presence of sodium

borohydride gave the desired 3°-amine **56**, the hydroxyl group within which was subjected to an Appel reaction using Ph_3P/CBr_4 and so affording bromide **57** (61% over two steps).

With compound **57** to hand we hoped that on treating it with tri-*n*-butyltin hydride this would form, through homolysis of the associated C–Br bond, the corresponding 1°-radical that would, in turn, engage in a 7-exo-trig cyclization reaction and so generating the D-ring of galanthamine. Alas, this was not to be. So, when bromide **57** was subjected to the relevant conditions two unexpected events took place (Scheme 10). First of all, the initially formed radical **58** participated in a spirocyclization onto the pendant and electron-rich arene residue and the resulting and extensively delocalized radical **59** then fragmented to give the nitrogen-stabilized congener **60** (overall a radical-based Smiles rearrangement) that now engaged in an 8-endo-trig radical cyclization to give isomer **61**.

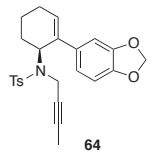


SCHEME 10: The Unexpected Radical-Based Reactions of the Tricyclic Iodide **57** – Formation of the D-Ring Galanthamine Isomer **63**.

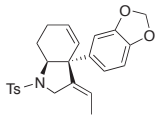
This latter mode of cyclization is presumably driven by the formation of a benzylic radical rather than a homobenzylic one (that would have arisen from the hoped for but unobserved 7-exo-trig cyclization process). Reduction of radical **61** would then deliver, after desilylation with TBAF, the observed dihydrobenzofuran **62** (<1%) while loss of a hydrogen atom from the former species would afford, again after a TBAF treatment, benzofuran **63** (12%). The structures of products **62** and **63** were established by single-crystal analyses. Given the latter is a D-ring isomer of galanthamine we wondered if it would act as an inhibitor of AChE. Molecular docking studies predicted it wouldn't because of the distinctly different molecular shapes of the two compounds and in the event this prediction was borne out – tetracycle **63** is not an effective inhibitor of the enzyme.[36]

6. Doing Things the Hard Way – *De Novo* Construction of the Aromatic C-Ring as a Focal Point

In 2010 we reported[38] that various nitrogen-linked 1,6-enynes including compound **64** engage in rather efficient palladium-catalyzed intramolecular Alder-ene (IMAE) reactions so as to generate angularly substituted polyhydroindoles such as **65**. Subsequently, we exploited this kind of transformation as a key step in the synthesis of the racemic modification of the crinine alkaloid hamayne.[39] A notable feature of these processes is the need to "cap" the alkyne residue of the substrate with, for example, a methyl group (as seen in **64**) so as to prevent competing hetero-dimerization reactions.

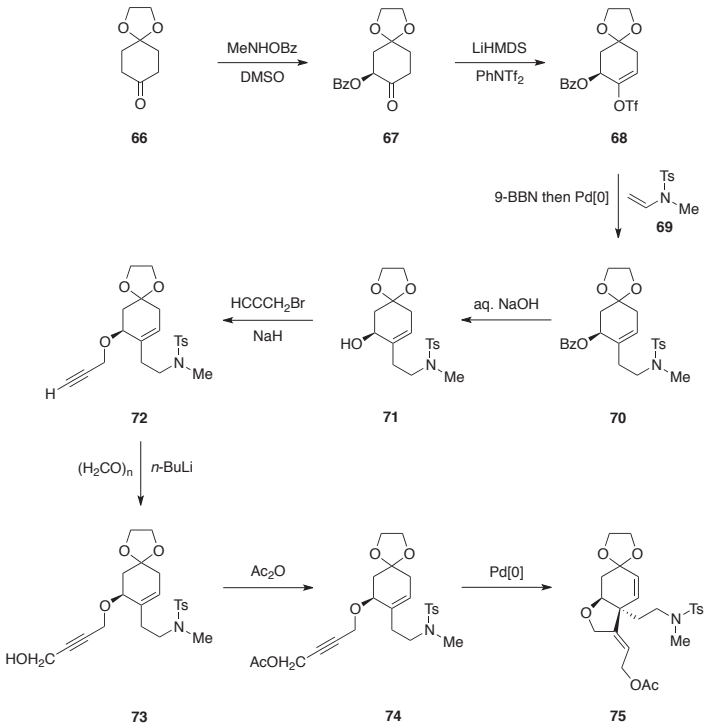


64



65

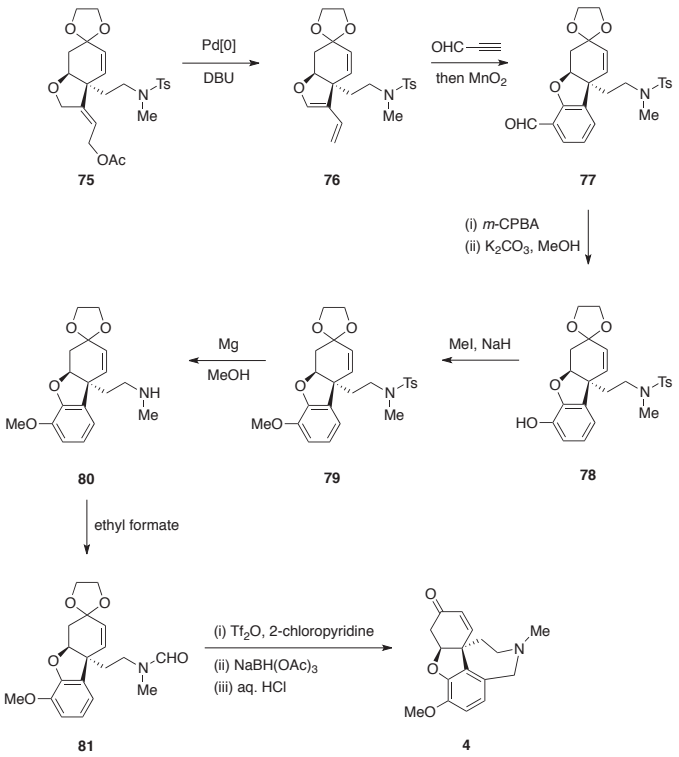
In seeking to understand the scope and limitations of such IMAE-based processes we wondered whether or not the corresponding oxygen-linked systems would undergo an analogous isomerization and thus affording angularly substituted perhydrobenzofurans related to the AB-ring system associated with galanthamine. It quickly became apparent that this was so as illustrated by the successful execution of the reaction sequence shown in Scheme 11.[40] Thus, the commercially available monoketal, **66**, of cyclohexane-1,4-dione was subjected to an α-oxidation protocol developed by Tomkinson and co-workers[41] and thus affording, in racemic form, the acyloin derivative **67** that was converted into the corresponding enol triflate **68** (73% over two steps) under standard conditions. Using a very effective procedure developed by Kamatani and Overman,[42] this last compound could then be cross-coupled with an organoborane derived from enamine **69** and so affording the β-aminoethyl-substituted compound **70** (79%). Saponification of the benzoate residue within the last compound proceeded uneventfully to give the corresponding alcohol **71** (71%) that was immediately reacted with propargyl bromide in the presence of sodium hydride to give the anticipated ether **72** (89%), the terminal alkyne moiety of which was "capped" by successive treatment with *n*-BuLi then paraformaldehyde and so giving the 1°-alcohol **73** (ca. 85%). This was then acetylated to give ester **74** (93%). Gratifyingly, on subjection to the types of conditions we have used previously for effecting IMAE reactions of related but somewhat simpler substrates, compound **74** could be efficiently isomerized to the benzofuran derivative **75** (71%).



SCHEME 11: The IMAE Route to the AB-Ring System of Galanthamine.

Compound **75** embodies the A and B rings of galanthamine as well as an angular substituent that could serve as a precursor to the D-ring. Of course, a significant challenge associated with seeking to exploit the results shown in Scheme 11 concerns the matter of incorporating the aromatic C-ring, a structural element that has been present from the outset in all previous syntheses of this alkaloid. As such, we became intrigued by the possibility that we could benzannulate compound **75** in some way and so assemble the requisite ABC-ring substructure by such means. Provided relevant protocols could be identified then novel C-ring variants of galanthamine might become accessible using this type of approach. In the event, and

as shown in Scheme 12, a suitable benzanulation protocol was identified and a synthesis of (–)-galanthamine thereby established. Thus, treatment of allylic acetate **75** with a Pd[0] catalyst in the presence of the base DBU resulted in elimination of the elements of acetic acid and, thereby, formation of the electron-rich and semi-cyclic 1,3-diene **76** (85%). This was readily engaged in a regio-selective Diels–Alder reaction with propynal and the rather unstable primary adduct so-formed treated, *in situ*, with manganese dioxide to effect its aromatization and thereby generating benzaldehyde **77** (61%). Dakin oxidation of this last compound using *m*-CPBA and cleavage of the resulting formate using potassium carbonate in methanol then gave phenol **78** (69%) that upon *O*-methylation afforded ether **79** (quantitative) that now embodies the essential "elements" of the ABC-ring substructure of galanthamine. As such it proved to be a relatively simple matter to elaborate compound **79** to (±)-narwedine, an established precursor (+)- or (–)-galanthamine.[20] Specifically, then, treatment of this last compound with magnesium turnings in methanol resulted in cleavage of the sulfonamide residue and the ensuing 2°-amine **80** (83%) was then reacted with ethyl formate to give the expected amide **81** (quantitative). Finally, subjection of compound **81** to a modified Bischler–Napieralski reaction using triflic anhydride and 2-chloropyridine,[43] reduction of the resulting acyliminium ion with $NaBH(OAc)_3$ and a mild acidic work-up (to cleave the ethylene ketal moiety) gave (±)-narwedine (**4**) albeit in an as yet unoptimized yield of 24%.



SCHEME 12: Assembling the Aromatic C-Ring of Galanthamine Using Diels–Alder Cycloaddition Chemistry and Completion of a Synthesis of (±)-Narwedine (**4**)

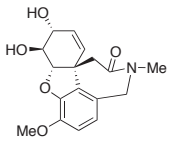
7. Conclusions

Only one of the synthetic sequences reported above has any reasonable prospect of providing an especially useful route to (–)-galanthamine and that is the so-called second-generation chemoenzymatic approach shown in Scheme 8. This was inspired by our work on the ribisins. Of course, and almost by definition, this chemistry was informed by the lessons learnt during the course of developing its first-generation counterpart. Currently the IMAE approach to the title alkaloid, as outlined in Schemes 11 and 12, is too long to be a useful means for obtaining significant quantities of galanthamine. However, and regardless of whether

refinements of it give any cause to change this assessment, it offers the capacity to construct novel aromatic C-ring analogues that might act as even more effective AChE inhibitors than (−)-galanthamine. As such it provides a quite distinct, if not a unique approach to the galanthamine framework.

In each of the instances discussed above, the successful construction of the D-ring associated galanthamine has relied on engaging an angular β-aminoethyl moiety (located at the junction between the A and B rings) in a Pictet–Spengler or Bischler–Napierlaski reaction. In two instances, the precursor to this moiety is obtained through an EC rearrangement reaction and several steps were necessary to convert the initially formed *N*,*N*-dimethylamide moiety into its mono-methyl counterpart. Clearly, then, there would be great merit in identifying a replacement for the dimethyl acetal of *N*,*N*-dimethylacetamide used in the EC rearrangement reaction with a species that generates the required mono-methylated amide directly. An even more attractive possibility would be to identify one that generates an acyl imminium ion immediately after the EC rearrangement and that thus engages in an *in situ* cyclization reaction to produce the D-ring directly. Such possibilities are under active investigation in our laboratories.

Another focus of efforts to extend our work in this area will be generating compounds such as **50** and the diol, **82**, derived from hydrolysis of bis-acetal **48**. These readily accessible systems could be regarded as hybrids of the ribisin and galanthamine structures[44] and might be expected to act as effective inhibitors of AChE. Certainly, as noted above, molecular docking studies suggest compound **50** should be active in this regard.



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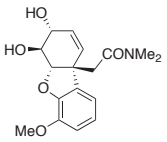

82

Regardless of the outcomes of the studies foreshadowed immediately above, it is clear that the intriguing molecular architecture of galanthamine has prompted a significant number of research groups to develop new strategies and tactics for its synthesis. Not all of these have been successful but in essentially every instance important lessons have been learnt along the way and these may well provide solutions to other, yet to be recognized challenges.

Acknowledgements

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Publication Two

Chemoenzymatic Pathways for the Synthesis of Biologically Active Natural Products

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Chemoenzymatic pathways for the synthesis of biologically active natural products

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Abstract

The whole-cell biotransformation of mono-nuclear aromatic compounds using certain genetically-engineered micro-organisms that over-express the enzyme toluene dioxygenase (TDO) allows for the large scale production of compounds known as *cis*-1,2-dihydrocatechols. These metabolites, which are normally obtained in enantiomerically pure form, can be manipulated, by chemical means, in a range of distinct (and predictable) ways with the result that they have proven to be especially versatile starting materials for the assembly of a range of structurally diverse and biologically active systems. Herein we describe, on a case-by-case basis, the recent applications of various combinations of TDO-mediated and chemical steps in so-called chemoenzymatic total syntheses of a range of organic compounds with therapeutic potential.

Introduction

Chemical space (*viz.* the space spanned by all possible small molecules and chemical compounds) is essentially infinite.[1] The challenge, then, has been to access the most meaningful or useful parts of it. Nature has provided critical inspirations. So, 3.8 billion years of evolution has produced a global molecular library of unsurpassed size, structural diversity and functional value – our planet's chemome.[2,3,4] Humankind has sought to "mine" this bioactive molecule resource for its benefit and such endeavors have been spectacularly successful as evidenced by the existence of the remarkable array of medicines, materials and agrochemicals that underpin society as we know it today. As a result the world we live in has been transformed. This is evidenced by our exploitation of drugs with household names such as penicillin, morphine and Taxol®. There are many additional but perhaps less well-known examples. For instance, organ transplant surgery would fail completely without the post-operative application of the chemome-derived anti-rejection drugs such FK506 and cyclosporin A.[5] Similarly, a significant number of agents that control agricultural pests, and so helping to ensure both the security and efficiency of world food production, have also come from Nature/the global chemome.[6]

Despite such successes, enormous challenges remain. So-called unmet scientific and societal needs include those arising from the development of resistance to current therapies (perhaps seen most prominently in the area of antibiotics[7]) and, in the

agrochemical sector, pest-control agents.[8] In addition, there is a desperate need for small molecule entities that provide, *inter alia*, effective control of neurodegenerative diseases and diabetes in a globally aging population, for ones that treat certain types of refractory cancers and for others that effectively modulate mammalian and other immune systems.

After forays into areas such as combinatorial chemistry,[9] major players in the pharmaceutical industry, sometimes in partnerships with Government-funded agencies, are returning to interrogation of the chemome (or at least portions thereof) as a means for productively probing chemical and thence biological space.[10] There are a number of reasons for such moves[10] including the recognition that, for example, the current pharmaceutical industry is built on <10% of the biosynthetic capacity of the microbial world, one that continues to show a remarkable ability to deliver biologically relevant small molecules.[11]

Occurring in tandem with these trends is the emergence of a plethora of new techniques and concepts concerned with the generation of biologically relevant molecular diversity involving the use of, *inter alia*, techniques of *de novo* biosynthesis for producing functionally annotated chemome components,[12] the creation of new metabolic pathways,[12] synthetic fermentation,[13] and activity-directed synthesis.[14] Simultaneously, new synergies are being recognized between *in vitro*, *in vivo* and *in silico* studies of drug metabolism [15] and thus allowing for much more efficient/rapid assessments of the utility of certain compounds as molecular probes, drugs and/or agrochemicals.

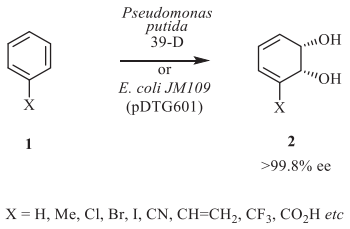
The development of new methods and protocols for effecting the chemical synthesis of biologically active natural products and various analogues remain important parts of the range of activities concerned with exploiting components of the global chemome for therapeutic and other purposes. At least two motivations drive such efforts, the first being the need to address issues of supply. Thus, it is often the case that secondary metabolites[2] are only available in miniscule amounts from their natural source with the result that insufficient material is available for development purposes. Chemical synthesis is often the best method for addressing such issues. Secondly, truly useful chemical syntheses offer the capacity to generate analogues of the natural product that would not normally be available through manipulation of the natural product itself.

This article, which is based on a lecture presented by the senior author at the University of Sydney as part of the RSNSW's 2014 Liversidge Award, details work being undertaken at the Australian National University on the exploitation of certain chemoenzymatic methods for the synthesis of biologically active natural products and their analogues. The work is presented according to the class of natural product being targeted as well as the structural and chemical relationships between them.

Results and discussion

The term chemoenzymatic synthesis used in this article, and elsewhere,[16] refers to the assembly of target compounds using a combination of chemical and enzymatic techniques. While there are many variations on this theme that reflect the extraordinarily diverse range of chemical and enzymatic transformations available these days, the specific form of the latter that applies here involves the whole-cell biotransformation of a range of simple and readily available aromatic compounds of the general form **1** (**Scheme 1**) into the corresponding *cis*-1,2-dihydrocatechols (**2**).[16] When genetically engineered micro-organisms such as *E. coli* JM109 (pDTG601)[17] are used for such

purposes, these metabolites can be readily produced at kilogram scales and are often obtained in >99.95 enantiomeric excess (ee). In the illustrated cases the enzyme responsible for these conversions is toluene dioxygenase (TDO) but a number of related ones are known including biphenyl dioxygenase, naphthalene dioxygenase and toluate dioxygenase. The end result is that a remarkable suite of *cis*-1,2-dihydrocatechols and related metabolites is known - these number in the many hundreds at the present time.[16c] Given the capacities to produce numerous mutants, and thus expand the range of substrates that can be biotransformed, the possible extensions of such processes would appear to be vast. A further fascinating aspect of them is the "chemoselectivities" they can display. So, for example, styrene (**1**, X = $CH{=}CH_2$) is converted into the triene **2** (X = $CH{=}CH_2$), a process wherein the aromatic ring is oxidised in preference to the exocyclic olefin, a functional group selectivity that cannot be achieved by any of the strictly chemical methods known at the present time.[18]



Scheme 1

The utility of the *cis*-1,2-dihydrocatechols (**2**) as starting materials in chemical synthesis has taken some time to be recognised in a broader sense. Various groups, especially those led by Ley in the UK[19] and Hudlicky in North America,[16a,d] have carried out the pioneering work in the area. Such studies established the reactivity "patterns" shown in **Figure 1** as well as attendant hazards arising from the dehydrative re-aromatisation of these substrates[20] and the propensity of certain derivatives, most notably the corresponding acetonides, to engage in normally unproductive Diels-Alder (DA) dimerization reactions.[21]

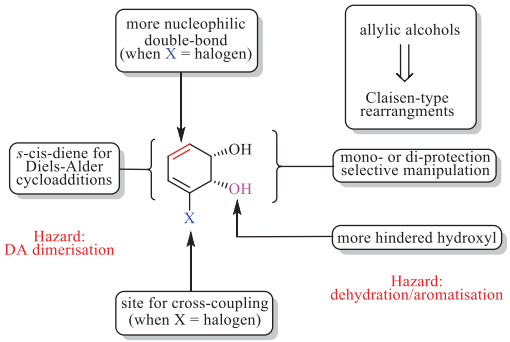


Figure 1

Our own contributions in the area began in the late 1980s[22] and in the intervening period we have been able to establish a series of total syntheses (**Figure 2**) that emphasise the extraordinary range of natural product targets available through manipulation of these metabolites. Some specific examples arising from our recent research are discussed on a case-by-case basis in the following sections.

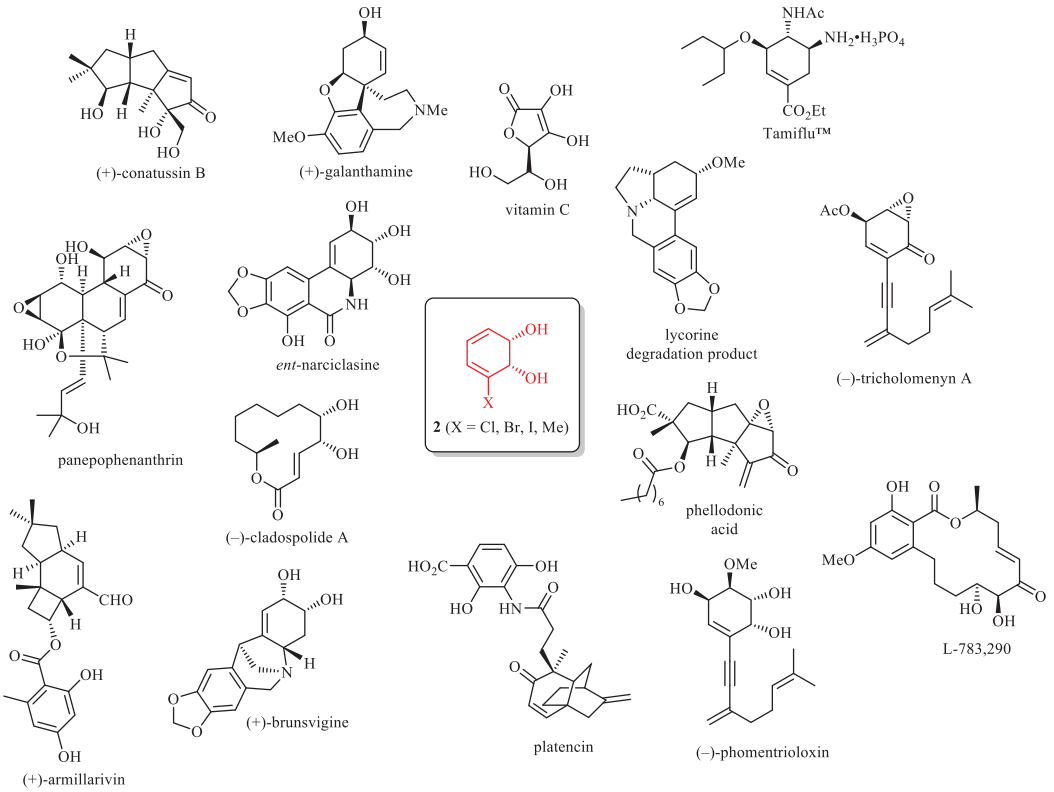


Figure 2

The Ribisins

Ribisins A-D were isolated by Fukuyama and co-workers from *Phellinus ribis* (Schmach.) Quél (Hymenochaetaceae),[23] a fungus used in traditional medicine for various purposes. Using a range of spectroscopic methods they were assigned structures **3**-**6** (**Figure 3**), respectively, and shown to enhance neurite outgrowth in PC12 cells at *ca.* 1 μM concentrations. As such they have potential for development as agents for the treatment of certain neurological disorders.

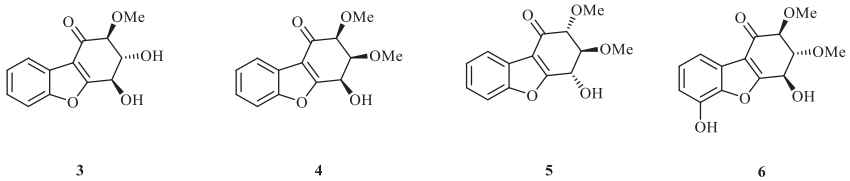
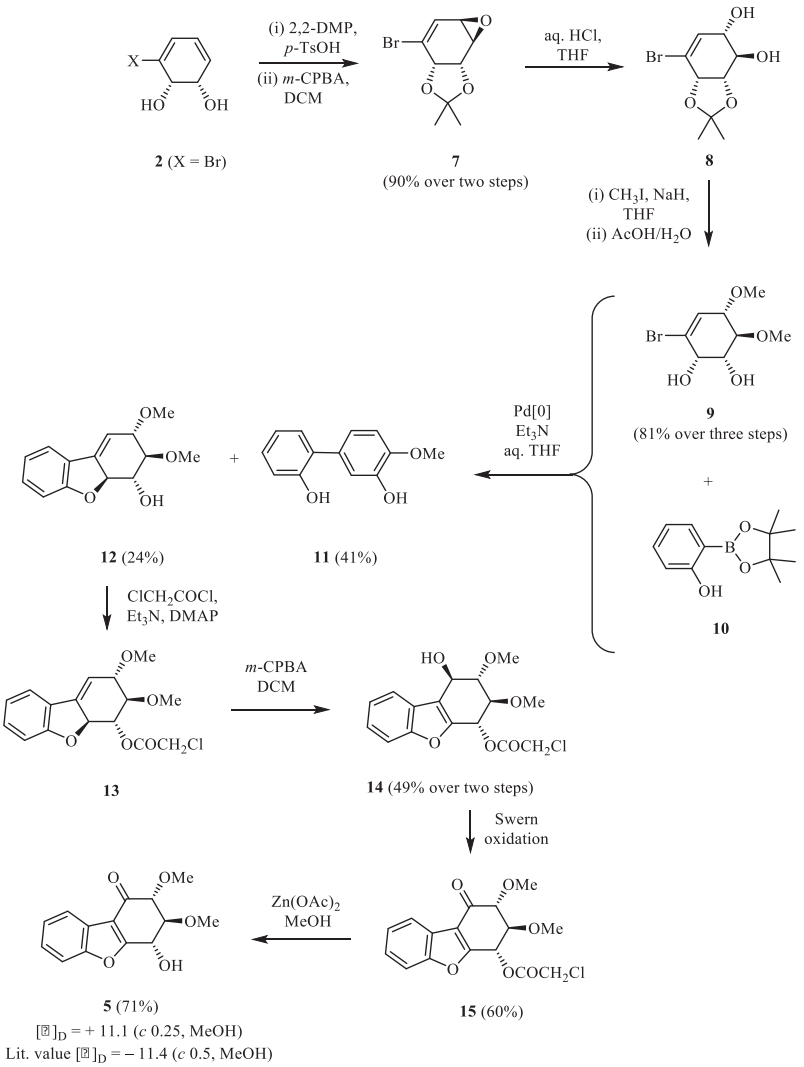


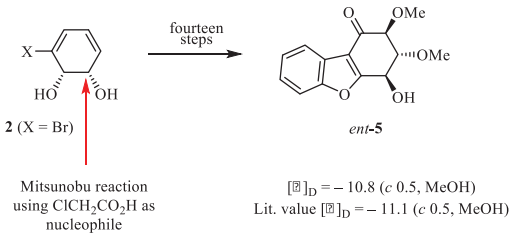
Figure 3

Given the structural resemblance of the polyoxygenated cyclohexane ring of these natural products to the *cis*-1,2-dihydrocatechols **2** (X = Br) we sought a means for effecting the relevant chemical conversions. The route used for establishing a synthesis of compound **5**, the structure assigned to ribisin C and the most active compound in the series, is shown in **Scheme 2**.[24]



Scheme 2

The opening stages of this reaction sequence are typical of the manner in which the *cis*-1,2-dihydrocatechols can be manipulated and involve the initial conversion of compound **2** (X = Br) into the corresponding acetonide and the regio- and stereo-selective epoxidation of the latter to give the oxirane **7**. Treatment of compound **7** with aqueous mineral acid resulted in a regioselective ring-opening reaction to afford the *trans*-diol **8** that could be bis-*O*-methylated under conventional conditions and the resulting acetonide was then cleaved, again under conventional conditions, to give the *cis*-diol **9** that embodies most of the key elements of the Eastern hemisphere of target **3**. Compound **9** could be engaged in a Suzuki-Miyaura cross-coupling reaction with the commercially available boronate ester **10** and two products thereby formed, namely the bis-phenol **11** and the dihydrobenzofuran **12**. Product **12** is presumably formed through cyclisation of the initially produced cross-coupling product while congener **11** arises from successive loss of the elements of water and methanol (no particular order implied) from the same intermediate. The lone hydroxyl group within compound **11** could be protected as the corresponding α-chloro-acetate **13**, a necessary step because of the looming introduction of a second hydroxyl group as the precursor to the ketone moiety. The use of the α-chloroacetate as a protecting group proved essential as in the final step of the reaction sequence attempts to remove the less labile parent acetate resulted in decomposition of the substrate. Epoxidation of compound **13** using *m*-chloroperbenzoic acid (*m*-CPBA) led, presumably *via* spontaneous rearrangement of the initially formed oxirane, to the benzofuran alcohol **14** that could be oxidised to the corresponding ketone **15** under Swern conditions. Cleavage of the α-chloroacetate residue within this last compound was accomplished using zinc acetate in methanol and thus forming the target compound **5**. While all the usual spectroscopic data acquired on compound **5** matched those reported for ribisin C, the specific rotation derived from the synthetic material was of the same magnitude but the opposite sign to that reported for the natural product. The implications are clear – the structure of ribisin C is represented by structure *ent*-**5** rather than **5**. Since we required an authentic sample of ribisin C (*ent*-**5**) for biological testing, a synthesis of it was pursued. This could be achieved (**Scheme 3**) using the same starting material and many of the same transformations as employed in generating its enantiomer (**5**). A key step of the fourteen-stage reaction sequence involved the inversion of configuration at C3 within a derivative of compound **2** (X = Br) using Mitsunobu chemistry. As a result ribisin C was obtained and all of the derived data, including the specific rotation, matched those reported for the natural product.



Scheme 3

Extensions of this sort of chemistry enabled the synthesis of all of the structures originally assigned to the ribisins and thus revealed that while ribisins A and D are constituted as originally described[23] that attributed to congener B is, like C, incorrect.[25] The true structures of all the ribisins are shown in **Figure 4** with the corrected stereocentres within compounds B (**16**) and C (*ent*-**5**) highlighted in red. Extensive biological evaluations of the ribisins and the range of

congeners prepared during the course of our synthetic studies are now underway.

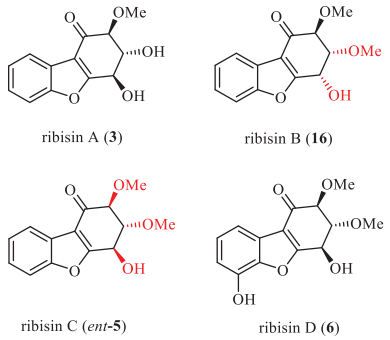


Figure 4

Analogues of Galanthamine

Ribisin D (**6**) bears a "provocative" structural resemblance to the ABC ring-system of the alkaloid galanthamine (**17**) that is used in many countries for the symptomatic treatment of Alzheimer's disease (**Figure 5**).[26] As such we were prompted to explore means by which the chemistry described above could be adapted so as to produce compounds bearing greater similarities to galanthamine (or, in the first instance at least, the enantiomer thereof).

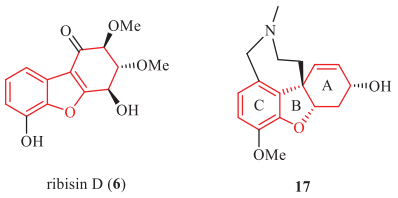
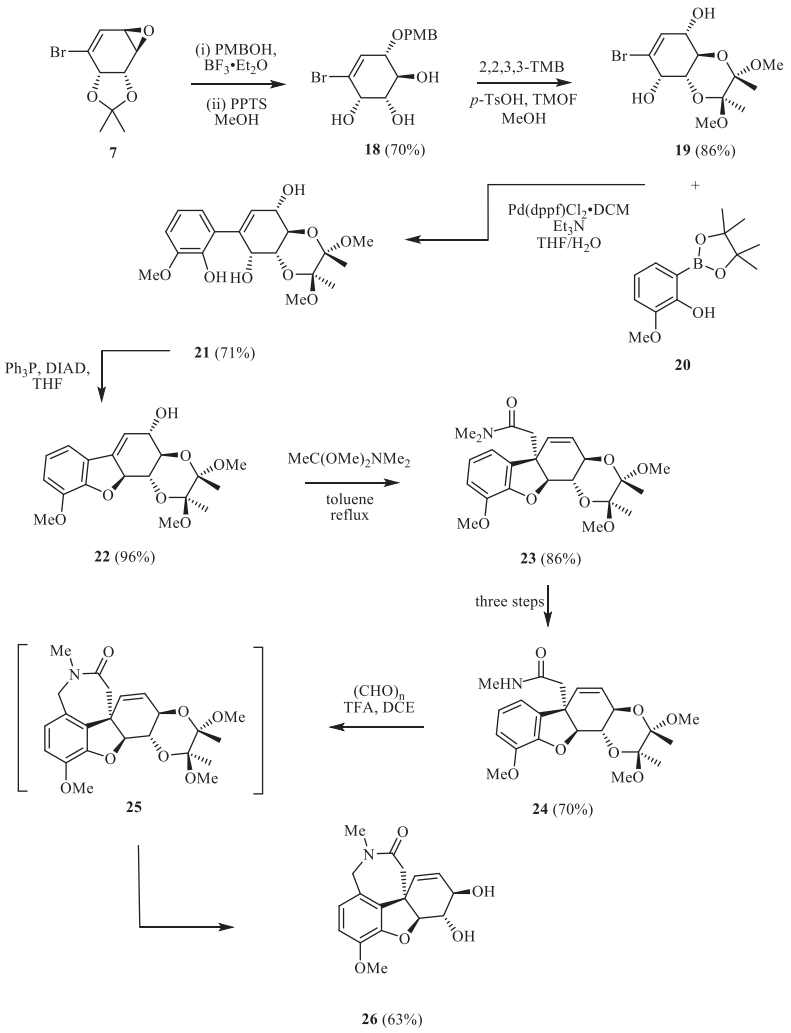


Figure 5

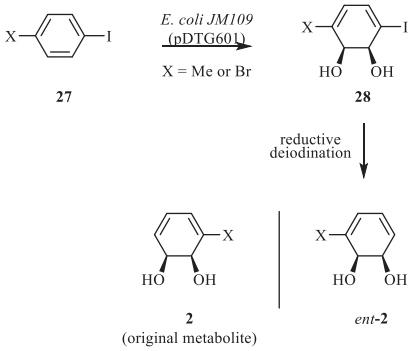
An efficient reaction sequence leading to a dioxygenated derivative of *ent*-galanthamine is shown in **Scheme 4**[27] and involves an initial reaction of the abovementioned oxirane **7** with *p*-methoxybenzyl alcohol (*p*-MBOH) in the presence of boron trifluoride diethyl etherate to generate the anticipated addition product that upon treatment, in a second step, with methanol containing pyridinium *p*-toluenesulfonate (PPTS) affords triol **18**. This last compound could be converted into the corresponding Ley ketal **19**[28] through treatment with 2,2,3,3-tetramethoxybutane (2,2,3,3-TMB) in the presence of *p*-toluenesulfonic acid (*p*-TsOH)/trimethyl orthoformate (TMOF) and Suzuki-Miyaura cross-coupling of this with the boronate ester **20** (produced directly from *o*-methoxyphenol using a C-H functionalization protocol) afforded the arylated cyclohexene **21**. This last compound that was itself engaged in an intramolecular Mitsunobu reaction using di-*iso*-propyl azodicarboxylate (DIAD) to afford the dihydrobenzofuran **22**.

Despite the potential for aromatisation (through simple double-bond migration), compound **22** could be engaged in an Eschenmoser-variant of the Claisen rearrangement reaction using the dimethyl acetal of *N*,*N*-dimethylacetamide[29] and thus affording the angularly substituted ABC-ring analogue **23** of *ent*-galanthamine. Over three conventional steps compound **23** could be converted into its mono-methylated counterpart **24**. The last compound participated in a Pictet-Spengler cyclisation reaction on exposure to a mixture of paraformaldehyde and trifluoroacetic acid (TFA) and the presumably first-formed product **25** underwent cleavage of the Ley acetal residue to give diol **26** as the only isolable product of reaction. Compound **26**, representing a dioxygenated derivative of *ent*-galanthamine (*ent*-**17**), and various congeners that have been prepared using related reaction sequences are currently being subjected to evaluation as inhibitors of the neurologically significant enzyme acetylcholine esterase (AChE).



Scheme 4

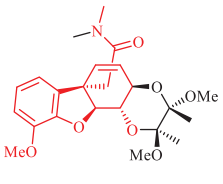
It is worth noting, at this point, that the enantiomer of certain of the *cis*-1,2-dihydrocatechols described above are also available.[30] So, for example, biotransformation of *p*-iodotoluene or *p*-iodobromobenzene [**27a** (X = Me) and **27b** (X = Br), respectively] (**Scheme 5**) using *E. coli* JM109 (pDTG601) affords metabolite **28** that upon exposure to dihydrogen in the presence of palladium on carbon undergoes hydrogenolytic cleavage of the associated C-I bond and thus delivering either *cis*-1,2-dihydrocatechol *ent*-**2** (X = Me) or *ent*-**2** (X = Br).



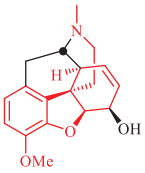
Scheme 5

The Opiates

Morphine and its congener codeine are members of opiate family. They are used extensively for the management of pain and represent the most widely applied and highest grossing medicines in the world today.[31] Their structural complexity means that for the moment, at least, opiates such as morphine are obtained from natural sources and then derivatized by simple chemical means so as to produce related drugs. Nevertheless, much progress has been made in terms of developing commercially viable total syntheses of these systems. Hudlicky and co-workers have defined the current "gold standard" in the area.[32] Given the tantalising structural resemblance between the readily available compound **23** and *ent*-codeine (**29**) (**Figure 6**) we are now attempting to modify the synthesis of the former so as to access the latter. This will likely involve introducing the necessary additional two-carbon unit by using a variant of boronate ester **20** and completing the synthesis of the less functionalised cyclohexane ring within target **29** using an intramolecular S_N' reaction that simultaneously cleaves the Ley acetal subunit.



23



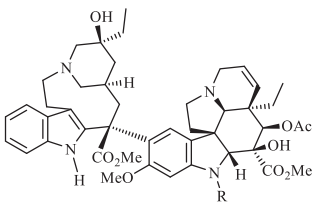
29
(ent-codeine)

Figure 6

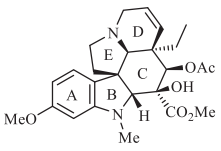
Vinblastine, Vincristine and Vindoline

Vinblastine (**30**) and vincristine (**31**) (**Figure 7**) are indole-indoline-based alkaloids derived from various plant sources, perhaps most notably the Madagascan rosy periwinkle.[33] They are used in the clinical treatment of non-Hodgkin's lymphomas as well as testicular, breast and lung cancers. These compounds are derived *in vivo* from the significantly more abundant and co-occurring alkaloid vindoline (**32**). Given the development of direct, chemically based and "bio-inspired" methods for effecting the conversion of this simpler compound into alkaloids **30** and **31**, vindoline has become the focus of considerable attention as a synthetic target.[34]

Our own efforts in this area have been inspired by the observation (**Figure 8**)[35] that the mutant organism *P. putida* BGXM1 can effect, in an enantioselective fashion, the whole-cell biotransformation of abundant *m*-ethyltoluene (**33**) into the carboxylic acid diol **34** that bears a striking resemblance to the highly functionalised C-ring of vindoline. Accordingly, a recent focus of some of our work in the area of chemoenzymatic synthesis has been on identifying methods for converting this metabolite into vindoline (**32**) and thence into vinblastine (**30**) and vincristine (**31**).



30 (R=Me)
31 (R=CHO)



32

Madagascan rosy periwinkle

Figure 7

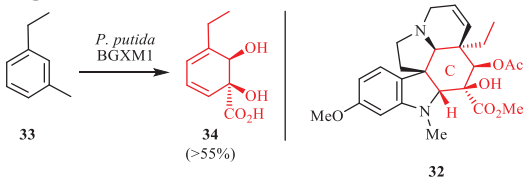
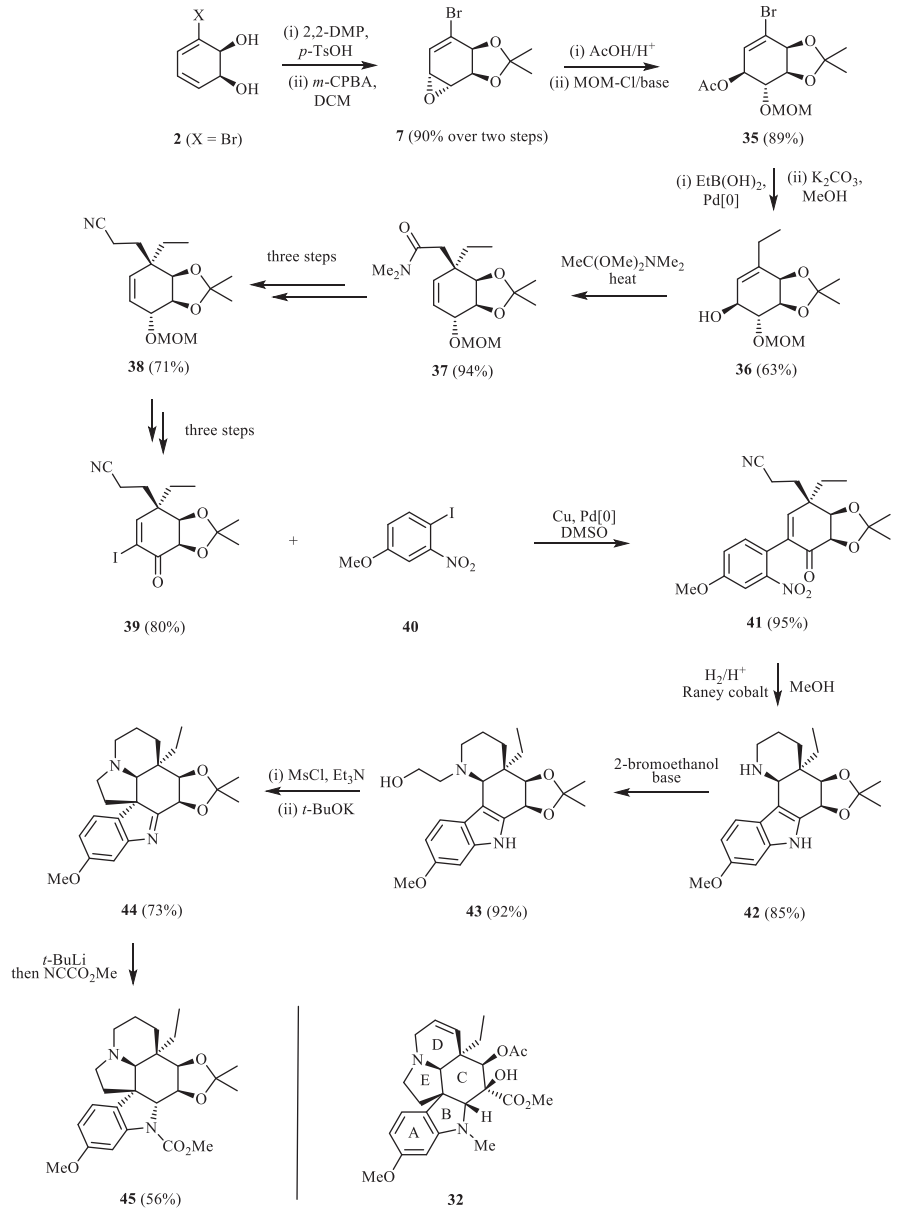


Figure 8

The model study outlined in **Scheme 6** has provided encouragement.[36] Thus, the *cis*-1,2-dihydrocatechol **2** (X = Br), representing a model for congener **34**, was converted, by the means described earlier, into the oxirane **7**. Treatment of this last compound with acetic acid in the presence of mineral acid afforded a *trans*-diol mono-ester that was protected under standard conditions as the corresponding MOM-ether and thus affording compound **35** that could be cross-coupled with ethyl boronic acid in the presence of a Pd[0] catalyst to give, after completing cleavage of the acetate residue using methanolic potassium carbonate, the allylic alcohol **36**. This last compound was engaged in a sluggish Eschenmoser-Claisen rearrangement reaction to give amide **37**, the side-chain of which could be elaborated, over three steps, into the nitrile **38**. Over a further three conventional steps this was converted into the α-iodocyclohexenone **39** that itself served as a substrate for a palladium-catalysed Ullmann cross-coupling reaction[37] with *o*-iodonitroarene **40** and so delivering the α-arylated cyclohexenone **41**. On exposure to dihydrogen in the presence of Raney cobalt[38] and a proton source compound **41** engaged in a series of chemoselective reductions and two cyclisation reactions with the result that the tetracyclic compound **42** was formed. The completion of the synthesis of the pentacyclic framework of vindoline proved straightforward and involved reaction of the last compound with 2-bromoethanol in the presence of base, mesylation of the resulting alcohol **43** and treatment of the sulfonate ester so formed with potassium *tert*-butoxide to generate the isoindole **44**.

In an effort to introduce the carbomethoxy group associated with alkaloid **32**, compound **44** was subjected to successive treatment with *tert*-butyllithium then Mander's reagent ($NCCO_2Me$).[39] However, rather than obtaining the hoped-for *C*-carbomethoxylated imine, carbamate **45** was produced, presumably by a pathway whereby the *tert*-butyllithium acts as a hydride source[40] with the resulting indoline anion then reacting (at nitrogen) with the added electrophile. Efforts are now underway to adapt these chemistries so as to convert metabolite **34** into vindoline. The most challenging issue associated with doing so will be finding a means for introducing the C-C double bond incorporated within the D-ring of target **32**.



Scheme 6

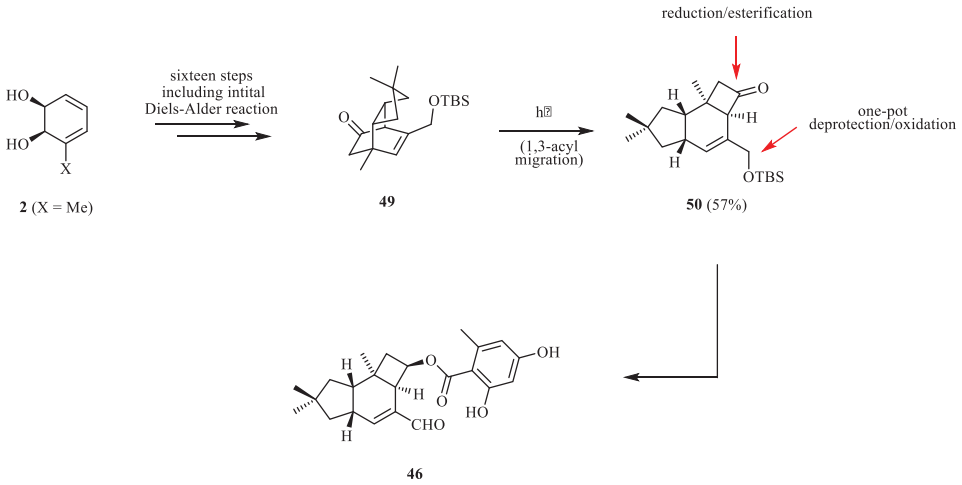
The Protoilludanes

The title sesquiterpenes embody a distinctive tricyclic framework wherein a central cyclohexane ring is annulated, in an angular arrangement, to both a four- and a five-membered ring.[41] The protoilludane aryl ester (+)-armillarivin (**46**) (**Figure 9**) has been found in the edible sugar mushroom *Armillaria mellea*[42] while representative additional natural products in this family include **47**[43] and **48**[44] that are derived from the saprotrophic wood decomposing fungus *Granulobasidium vellereum* (Ellis & Cragin) Jülich.

Figure 9

In 2013 we described the first and thus far only total synthesis of (+)-armillarivin.[45] A key element of our approach (**Scheme 7**) was an initial high-pressure promoted and completely regio- and stereo-selective Diels-Alder reaction between the *cis*-1,2-dihydrocatechol **2** (X = Me) and cyclopentenone.[46] Relatively conventional but rather extensive manipulations of the resulting adduct lead to the cyclopentannulated bicyclo[2.2.2]octenone **49** that engaged, as a second pivotal step of the synthesis, in a photochemically-promoted 1,3-acyl migration reaction (Givens rearrangement)[47] to afford the tricyclic isomer **50**. This last compound, which embodies the tricyclic protoilludane framework, was readily manipulated over just three steps to deliver (+)-armillarivin. The structure of this synthetically produced material was confirmed by single-crystal X-ray analysis and all the derived spectroscopic data, including specific rotation, matched those reported for the natural product.

Subjection of the acetonide derivative of compound **2** (X = Me) to a Diels-Alder reaction with cyclopentenone affords, *via* addition of the dienophile to the face of the diene opposite to that "occupied" by the hydroxyl groups, cyclopentannulated bicyclo-[2.2.2]octenones that are enantiomerically related to those obtained by the pathway described immediately above. In essence, then, by controlling the facial selectivity of such cycloaddition reactions either enantiomeric form of the relevant Diels-Alder adduct can be obtained.



Scheme 7

By such means we have recently been able to complete total syntheses of the enantiomeric forms of the protoilludanes **47** and **48**[48] and thus confirming, for the first time, the structures assigned to them.

Platencin

The Diels-Alder cycloaddition chemistry involving *cis*-1,2-dihydrocatechols as the 4π-component can be effectively extended to intramolecular variants. This is perhaps best exemplified in our recently completed first- and second-generation chemoenzymatic syntheses of platencin (**51**),[49,50] a compound isolated from *Streptomyces platensis* MA7327 that acts as a potent and dual inhibitor of FabH and FabF, key enzymes associated with fatty acid biosynthesis in bacteria (**Figure 10**).[51] By virtue of its novel structure and modes of action, platencin is regarded as an important new lead in the development of urgently needed, next-generation anti-bacterial agents.[52]

In our first generation synthesis of compound **51** (**Scheme 8**),[49] the acetonide derivative, **52**, of the *cis*-1,2-dihydrocatechol **2** (X = I) was engaged in a Stille cross-coupling reaction with the *Z*-configured alkenylstannane **53** to give the tetra-ene **54**. Substrate **53** was prepared in a straightforward manner with the stereochemistry at the quaternary carbon centre being controlled through the agency of a chiral auxiliary.

While compound **54** failed to engage in an intramolecular Diels-Alder (IMDA) reaction, the readily derived ketone **55** did so when heated in refluxing toluene and thus affording, in stereochemically pure form, adduct **56** embodying the tricarbocyclic core of platencin. Over a further thirteen steps compound **56** could be converted into (–)-platencin (**51**).

Some of these steps were needed to deal with functional group incompatibilities, an issue that has been addressed, albeit in a modest way, through our recently disclosed second-generation synthesis.[50] In a developing collaboration with the Hudlicky group at Brock University (Canada), efforts are now focussed on a third-generation approach.

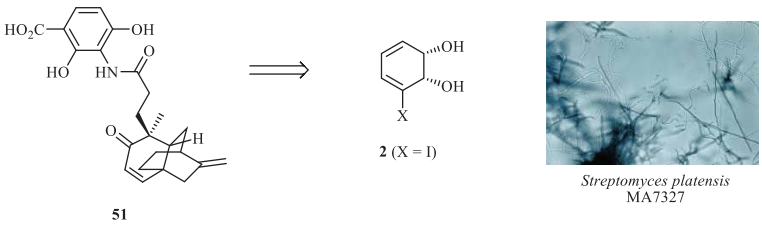
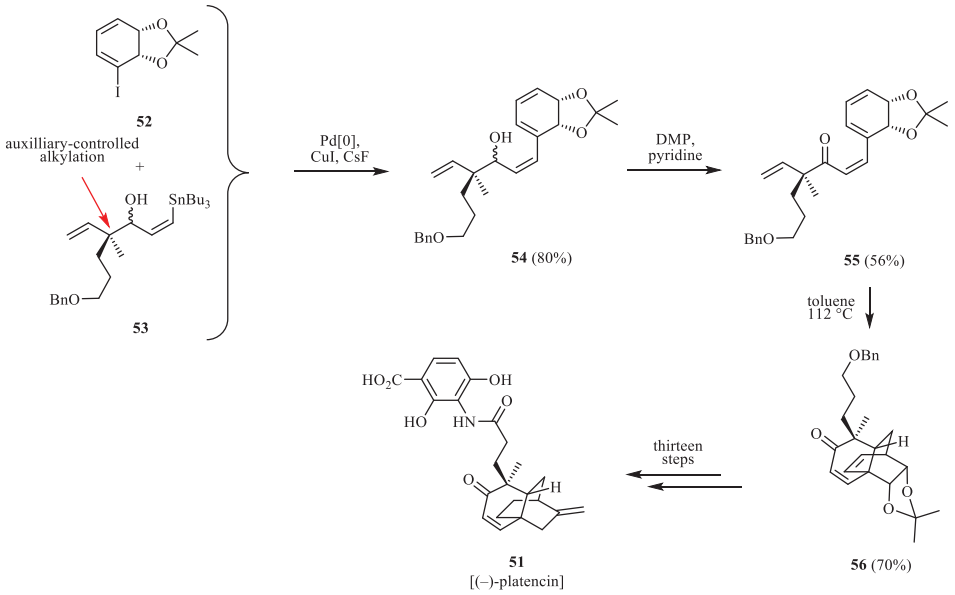


Figure 10



Scheme 8

Conclusions

Enzymes have an almost unparalleled capacity to transform simple organic substrates into synthetically more valuable ones, especially enantiomerically pure compounds (EPCs). Through the use of various genetic engineering, gene shuffling and directed evolution techniques the opportunities to expand upon the existing "library" of metabolites seem almost infinite. Furthermore, pathway-engineering techniques provide a capacity to produce (mutant) organisms that effect, through the orchestrated action of a series of enzymes, multistep transformations. The conversion of *m*-ethyltoluene (**33**) into compound **34**[35] is a case in point and wherein both mono-oxygenases and dioxygenases act in concert to produce a potentially high-value metabolite. When combined with the power of chemical synthesis (as manifest in the techniques of chemoenzymatic synthesis), such bio-transformations provide a powerful tool kit for preparing a wide range of compounds of biological relevance. Ironically, perhaps, while microbiologists have a remarkable capacity to generate a diversity of low molecular weight metabolites (and often at multi-kilogram or larger scale) and synthesis chemists have an almost insatiable appetite for new synthons, the often siloed nature of academic research activities results in less than desirable overlap of the relevant sets of expertise. Changing this situation can only benefit both disciplines.

Acknowledgements

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Publication Three

The Synthesis of Certain Derivatives and Analogues of (–)- and (+)-Galanthamine and an Assessment of their Capacities to Inhibit Acetylcholine Esterase

Joshua N. Buckler, Ehab S. Taher, Nicolas J. Fraser, Anthony C. Willis, Paul D. Carr, Colin J. Jackson and Martin G. Banwell

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The Synthesis of Certain Derivatives and Analogues of (−)- and (+)-Galanthamine and an Assessment of their Capacities to Inhibit Acetylcholine Esterase

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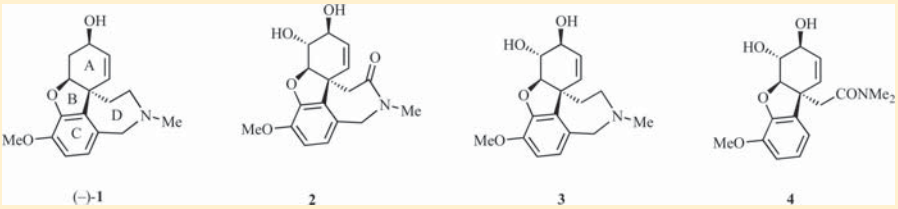
Supporting Information



ABSTRACT: Syntheses of certain di- and mono-oxygenated derivatives (e.g., **2** and **3**, respectively) and analogues (e.g., **4**, a D-ring monoseco-analogue of **2**) of both the (−)- and (+)-enantiomeric forms of the alkaloid galanthamine [(−)-**1**] are reported. All have been assessed for their capacities to inhibit acetylcholine esterase but, in contrast to the predictions from docking studies, none bind strongly to this enzyme.

INTRODUCTION

The alkaloid (−)-galanthamine [(−)-**1**] (Figure 1) has been isolated from a range of plant sources and is currently used in the clinic for the symptomatic treatment of mild to moderate forms of Alzheimer's disease.[1] It exerts its beneficial effects by crossing the blood-brain barrier and then, in part at least, inhibiting acetylcholine esterase (AChE). It also acts as an allosteric modulator of the nicotinic acetylcholine receptor.[1,2] The non-natural enantiomer of compound **1**, namely *ent*-**1** or (+)-galanthamine, has also been shown to accumulate in brain tissue but does so through nonspecific binding.[3]

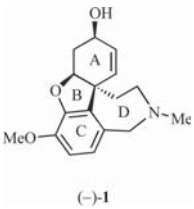


Figure 1. Structure of the alkaloid (−)-galanthamine.

Currently, (−)-galanthamine is produced industrially by extraction from various plants sources, most notably the red spider lily (*Lycoris radia*), the wild daffodil (*Narcissus pseudonarcissus*), the summer snowflake (*Leucojum aestivum*), and the Caucasian snowdrop (*Galanthus woronowii*).[1] However, both the increasing demands for the natural product and the erosion of habitat of at least some of the producing plants has prompted investigations into other methods for obtaining it or for identifying analogues with improved efficacy. As part of such efforts, galanthamine has been the subject of a significant number of total synthesis studies with the first of these being reported by Barton and Kirby[4] and involving mimicking of the proposed biogenesis. Substantial refinements of this process have been reported in the interim,[5] and one of these has formed the basis of a pilot-plant scale synthesis of the alkaloid[5a] although it is not clear if this contributes significantly to the commercial production of the alkaloid. Magnus and co-workers have described[6] a related and highly effective approach. Intramolecular Heck reactions have provided another means for assembling the tetracyclic framework of galanthamine,[7] including those accomplished in an enantioselective manner, while various chirons (corresponding to the A-ring) have been employed for the assembly in either enantiomeric form of the alkaloid.[8,9a] New routes to (−)-galanthamine continue to be reported,[1e] including approaches from our group.[9]

The identification and biological evaluation of analogues of galanthamine has been another focus of significant activity[10] that is now greatly assisted by data derived from high-resolution X-ray analysis of the alkaloid bound to the active site of acetylcholine esterase.[11] Biomimetic diversity-oriented syn-

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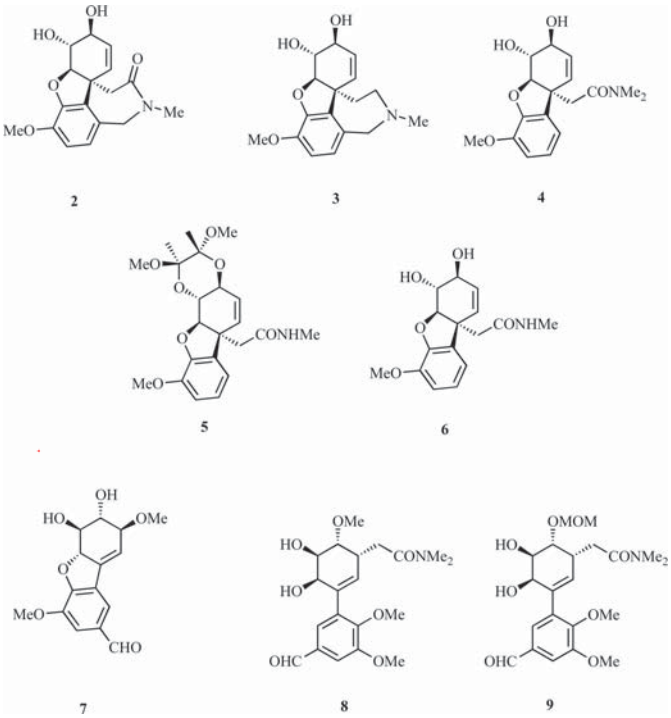

Figure 2. Galanthamine derivatives/analogues **2**–**9** targeted for synthesis.

thesis, sophisticated QSAR analyses, multicomponent-coupling chemistries, as well as more conventional studies have all revealed active compounds.[12] The screening of natural products for relevant activities remains an ongoing area of investigation and has also resulted in the isolation of new inhibitors of the title enzyme.[13]

As part of an ongoing program to establish concise routes to the tetracyclic framework of galanthamine,[1e,9] we now report chemoenzymatic syntheses of two oxygenated derivatives, **2** and **3**, as well as analogues **4**–**9** of the natural or (−)-form of the alkaloid (Figure 2).[14]

Syntheses of the enantiomers of the first five of these derivatives/analogues, namely compounds *ent*-**2** to *ent*-**6**, are also described. As detailed below, and contrary to the predictions arising from molecular docking studies, none of these is an effective inhibitor of acetylcholine esterase.

Our motivation for undertaking the studies described herein was that the introduction of additional functionalities within the galanthamine framework could increase water solubility and/or provide the means for conjugating the drug with various groups including peptide fragments[10f] or other entities (e.g. memantine)[10d] and thus allow for the development of a multi-targeted therapeutic approach.[10d] In principle, then, the attachment of such moieties could provide new inhibitors (or even just prodrug forms[10e] of galanthamine) that are superior to existing therapies. As revealed below, the nature of our synthetic strategy is such that additionally oxygenated forms of the galanthamine A-ring were likely to be the most readily accessible. Accordingly, and because this region of alkaloid has not been "explored" previously, such derivatives became a major focus of the work detailed below.

RESULTS AND DISCUSSION

Chemical Synthesis Studies. The reaction sequence used to assemble ABC-ring substructures of (−)-galanthamine is shown in Scheme 1 and employs the readily available L-tartaric acid (**10**) as starting material. Thus, as specified in a recent publication,[15] compound **10** can be converted over 11 steps, involving reduction, Grignard addition, and ring-closing metatheses as key transformations, into the 1,2-diacetal annulated bromocyclohexene **11**. Coupling of compound **11** with the readily available[16] aryl boronic acid ester **12** proceeded under conventional conditions to give the anticipated arylated cyclohexene **13** (68%). Following protocols established during the course of our syntheses of the ribisins,[17] this last compound was engaged in an intramolecular Mitsunobu reaction using triphenylphosphine in conjunction with di-*iso*-propyl azodicarboxylate (DIAD) wherein the phenolic hydroxyl group served as the internal nucleophile and so affording the acid-sensitive isobenzofuran **14** (33%). As demonstrated through work in the enantiomeric series (see below), if appropriate account is taken of this acid-sensitivity, then the Mitsunobu reaction can be a high yielding one. Despite concerns about the potential for competing isomerization of compound **14** to its more conjugated (fully aromatic) counterpart, upon subjecting it to conditions previously employed for effecting the Eschenmoser–Claisen rearrangement of allylic alcohols,[18] amide **15** was produced in 84% yield. The structure of this compound followed not only from the derived NMR, IR, and mass spectral

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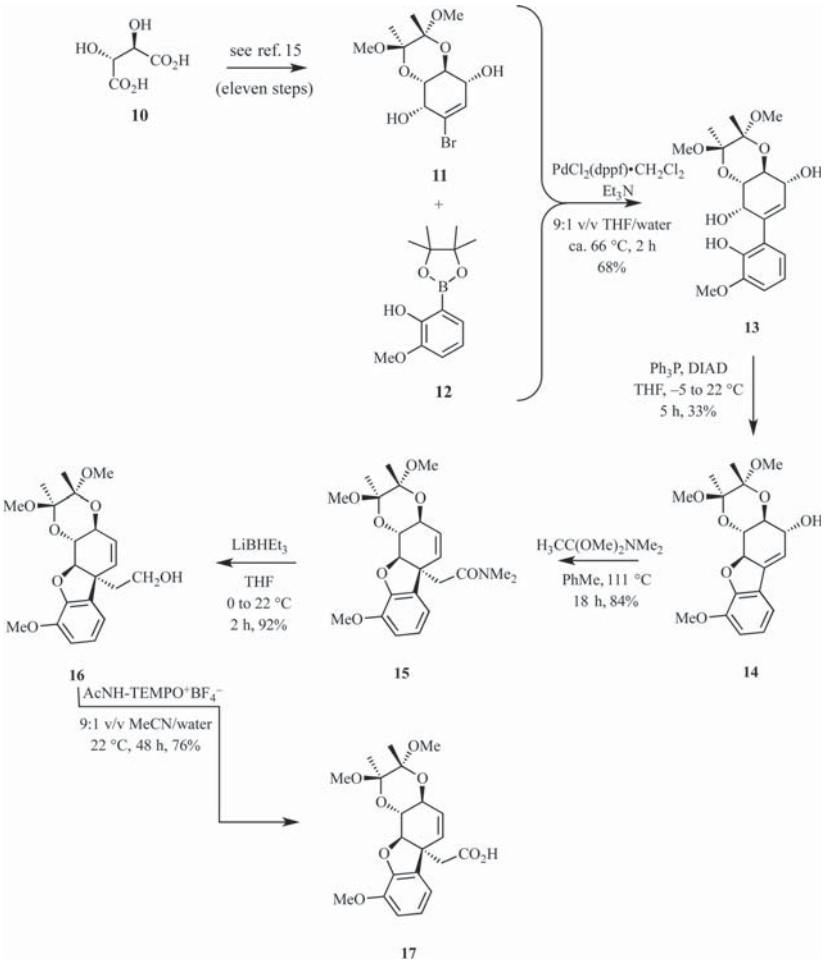
Scheme 1. Synthesis of Key Acid 17 Embodying the ABC-Ring Substructure and Associated Quaternary Carbon of (−)-Galanthamine



data but also from a single-crystal X-ray analysis of its enantiomer (see below). Compound **15** embodies both the targeted ABC-ring substructure of (−)-galanthamine and the associated quaternary carbon. In anticipation of installing the final D-ring of the title alkaloid, the amide residue within compound **15** was reduced using $LiBHEt_3$ and 1° alcohol **16** thereby obtained in 92% yield. Oxidation of compound **16** under conditions defined by Bobbitt and Bailey[19] then gave acid **17** (76%), which represents the key precursor to the targeted galanthamine derivatives/analogues **2**−**6**.

The straightforward manipulations of acid **17** leading to the targeted (−)-galanthamine derivatives/analogues **2**, **3**, **5**, and **6** are shown in Scheme 2. Thus, coupling of compound **17** and methylamine, using 1,1′-carbonyldiimidazole (CDI) for activation of the acid, afforded amide **5** (79%), and on exposure of the latter to modified Pictet−Spengler conditions[7c,20] involving paraformaldehyde in the presence of trifluoroacetic acid (TFA), tetracyclic lactam **2** (47%) was formed as a result of concomitant cleavage of the Ley acetal moiety. Upon treatment with sodium bis(2-methoxyethoxy)aluminum dihydride, compound **2** was reduced to azepine **3** (44%), and hydrolysis of the 1,2-diacetal residue within compound **5** using aqueous trifluoroacetic acid (TFA) afforded diol **6** (66%). Compound **6** can be considered as a hybrid of the title alkaloid and the neurologically active natural product ribisin D.[17,21]

The synthesis of compound **4**, a monoseco derivative of 5*R*-hydroxy-(−)-galanthamine (**3**), simply involved (Scheme 3) acid-catalyzed hydrolysis of precursor **15** under conventional conditions. This reaction proceeded in 88% yield.

All of the spectral data obtained on targeted compounds **2**−**6** were in complete accordance with the assigned structures but final confirmation of that of the first (i.e., **2**) followed from a single-crystal X-ray analysis of its enantiomer (see below).

In an effort to establish a more meaningful SAR profile for the above-mentioned analogues, the enantiomerically related derivatives/analogues *ent*-**2** to *ent*-**6** (Figure 3) were sought.

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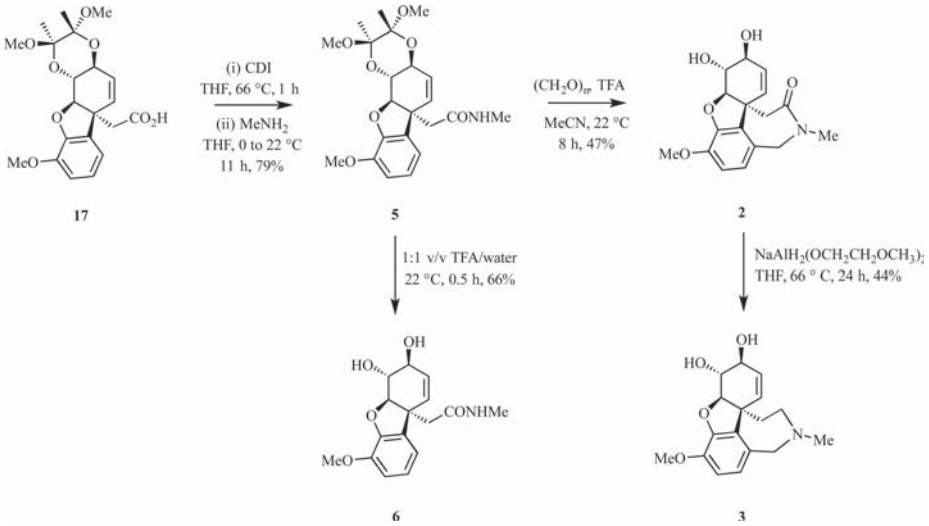
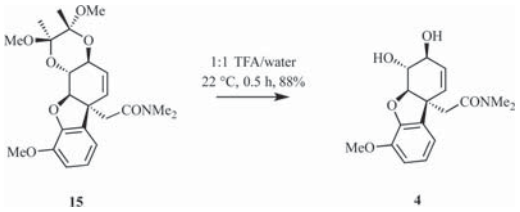
Scheme 2. Conversion of Acid 17 into the (−)-Galanthamine Derivatives/Analogues 2, 3, 5, and 6



Scheme 3. Hydrolysis of Biacetal 15 Leading to Compound 4



Although the routes defined above could simply be adapted for this purpose by starting with D- rather than L-taratric acid, we were able to establish a shorter pathway by starting with an enzymatically derived chiron that is readily available in the required enantiomeric form (but less so in the opposite one required to prepare the derivatives/analogues just described).

The synthesis of the enantiomeric series of compounds started, as shown in Scheme 4, with the enzymatically derived and enantiomerically pure *cis*-1,2-dihydrocatechol **18**[22] that was converted into the corresponding and well-known[23] acetonide **19** under standard conditions. Immediate treatment of the last compound with *m*-chloroperbenzoic acid (*m*-CPBA) then afforded, in a completely regio- and stereo-selective fashion, epoxide **20**[23] (93% from **18**). Reaction of compound **20** with a large excess of *p*-methoxybenzylalcohol (*p*-MBnOH) in the presence of boron trifluoride etherate ($BF_3{\cdot}Et_2O$) resulted in selective nucleophilic opening of the epoxide ring at the allylic

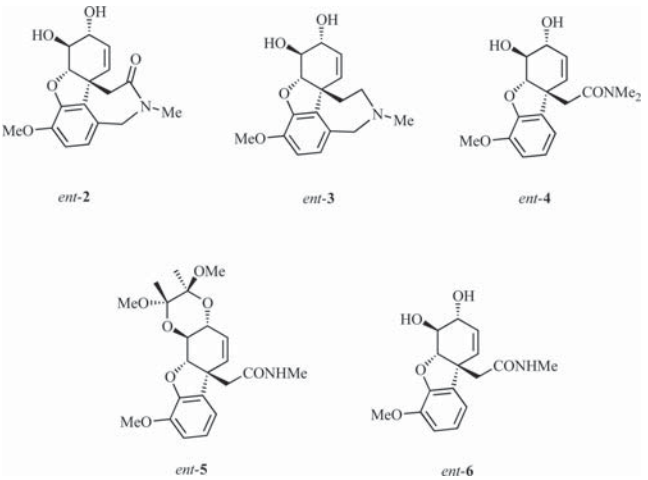


Figure 3. Enantiomeric series of derivatives/analogues.

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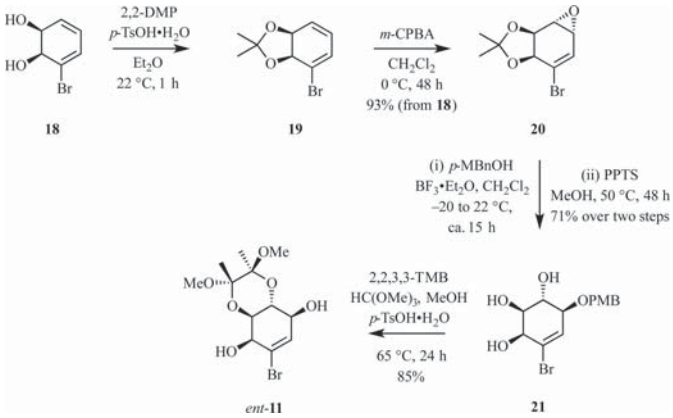
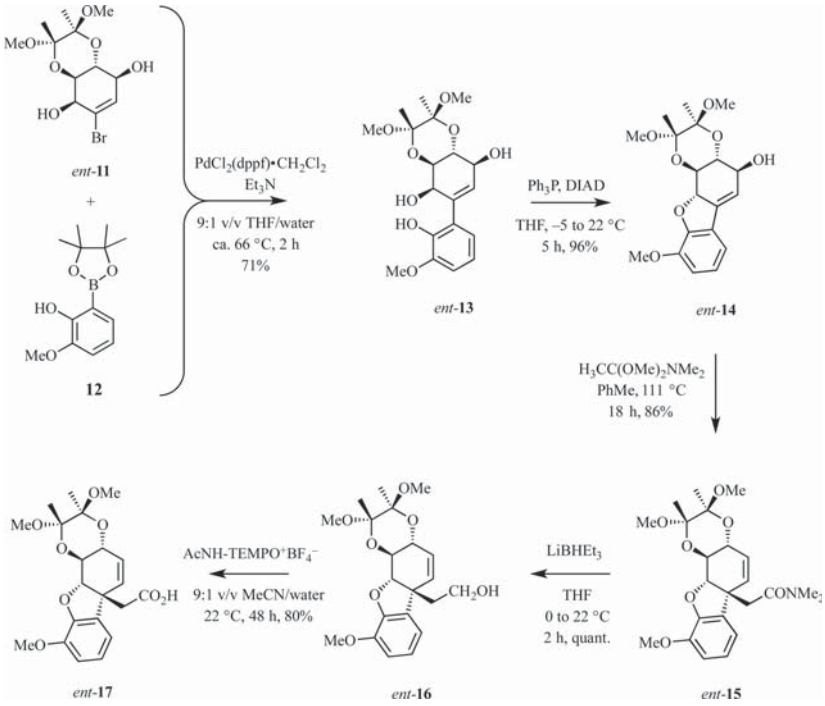
Scheme 4. Synthesis of Bromoconduritol *ent*-11 from the Enzymatically-Derived and Homochiral *cis*-1,2-Dihydrocatechol



Scheme 5. Synthesis of Key Acid *ent*-17 from Bromoconduritol *ent*-11



carbon,[24] but the protected bromoconduritol thus formed was not isolated. Rather, it was simply allowed to react with methanol in the presence of pyridinium tosylate (PPTS) and thereby affording triol **21** (71%). Treatment of a methanolic solution of this last compound with 2,2,3,3-tetramethoxybutane (2,2,3,3-TMB) in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) then resulted in the selective formation of the "Ley"-acetal[25] *ent*-**11** (85%) and so establishing an "enantiomeric overlap" with the synthetic sequence leading to the original sets of analogues.

During the conversion, **21** → *ent*-**11** acetal formation is presumed to take place prior to cleavage of the PMB-ether unit because the reverse order of events would lead to an intermediate conduritol embodying two adjacent *trans*-diol moieties and the formation of two isomeric Ley-type acetals would therefore be expected. Indeed, when the tetra-ol derived from hydrolysis of compound **21** was subjected to reaction with 2,2,3,3-TMB in the presence of *p*-TsOH·H_2O then an ~1:1 mixture of the two possible bis-acetals is formed.

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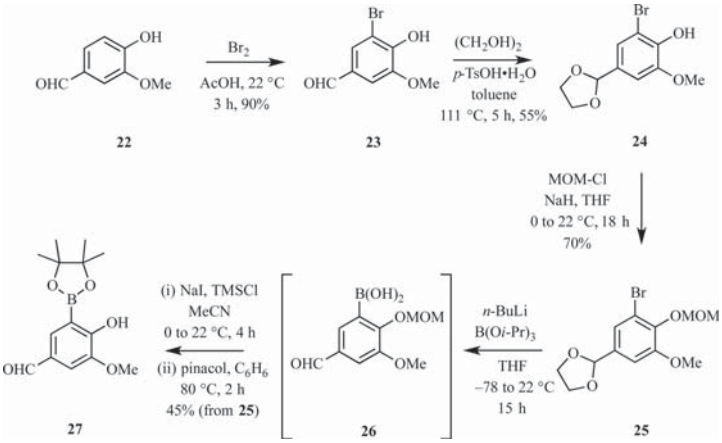
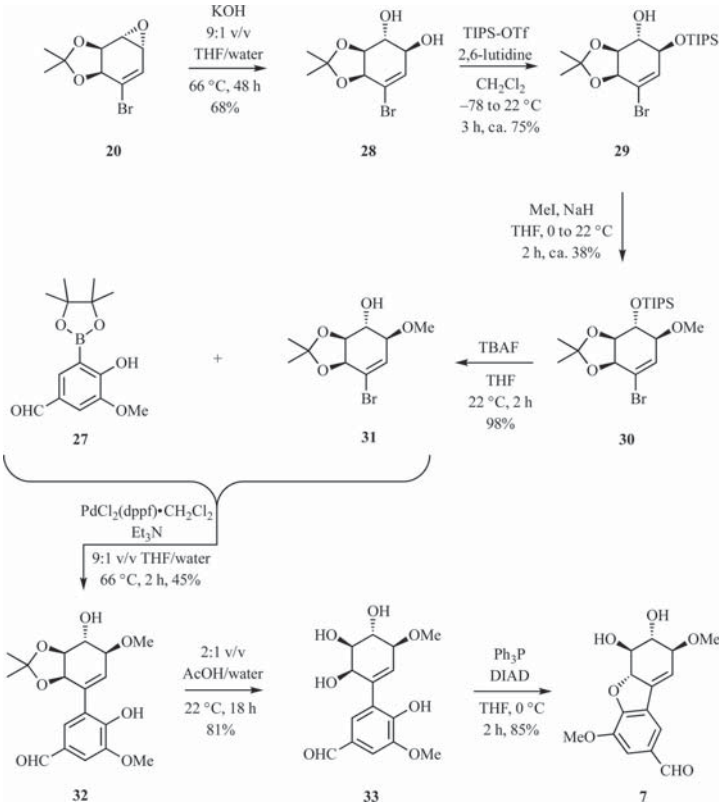
Scheme 6. Synthesis of Aryl Boronate Ester 27



Scheme 7. Synthesis of Analogue 7



As shown in Scheme 5, and as was the case in the enantiomeric series, compound *ent*-**11** could be engaged in a Suzuki–Miyaura cross-coupling reaction[26] with arylboronic acid ester **12**, thus affording the anticipated product *ent*-**13** (71%) that participated in an intramolecular Mitsunobu reaction to give compound *ent*-**14** (96%). Allylic alcohol *ent*-**14** underwent an Eschenmoser–Claisen rearrangement reaction on thermolysis with the dimethyl acetal of *N*,*N*-dimethylacetamide in refluxing toluene and thereby affording *N*,*N*-dimethylamide *ent*-**15** (86%). The structure of this last

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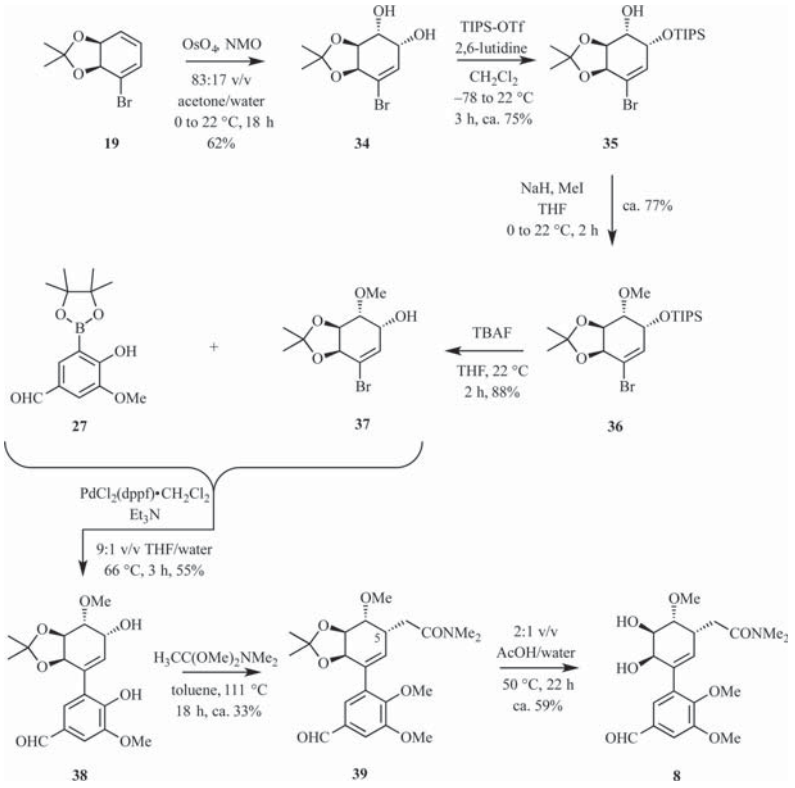
Scheme 8. Synthesis of Analogue 8



compound was confirmed by a single-crystal X-ray analysis, details of which are provided in the Experimental Section and the Supporting Information (SI). Reduction of compound *ent*-**15** with lithium triethylborohydride and oxidation of the resulting 1° alcohol *ent*-**16** (quant.) using the Bobbitt–Bailey protocol[19] then gave acid *ent*-**17** (80%).

Following precisely the same reaction sequences as detailed above in Schemes 2 and 3, compound *ent*-**17** was converted into target derivatives *ent*-**2** to *ent*-**6** (Figure 3) with the structure of the first of these being confirmed by single-crystal X-ray analysis. The monoseco analogue of compound *ent*-**2**, namely amide *ent*-**4**, was readily obtained in 77% yield by simply treating bis-acetal *ent*-**15** with aqueous trifluoroacetic acid (compare to Scheme 3).

As part of an effort to develop galanthamine derivatives containing additional functionality in the aromatic C-ring, especially ones capable of conjugation with motifs that might bind to the so-called peripheral and anionic binding site of acetylcholine esterase,[27] we sought to exploit the synthetic chemistry detailed above for this purpose. As such, the relevant arylboronate acid ester (representing a synthon for the C-ring) was required and the route used to obtain this is shown in Scheme 6. Thus, vanillin (**22**) was converted, under established conditions, into its bromo-derivative **23**[28] (90%), and the aldehydic residue within the latter then protected as the corresponding ethylene acetal using standard conditions and thus affording compound **24** in 55% yield. The readily derived MOM-ether **25** (70%) of the last compound was subjected to a metalation/borylation protocol, and the intermediate boronic acid **26** obtained on hydrolytic work up was reacted with sodium iodide/trimethylsilyl chloride (to cleave the MOM ether) and then pinacol and thus affording the hitherto unreported ester **27** (45% from **25**). The structure of this last compound was confirmed by single-crystal X-ray analysis (see Experimental Section and SI for details).

In the opening stages of attempts to exploit ester **27** in the production of galanthamine analogues related to those described above, epoxide **19** (Scheme 7) was subjected to hydrolytic cleavage, thus affording previously reported[29] *trans*-diol **28** (68%). The allylic hydroxyl group of diol **28** was selectively protected through its reaction with tri-*iso*-propylsilyl trifluoromethanesulfonate (TIPS-OTf) in the presence of 2,6-lutidine and thus producing allylic ether **29** (88%).[30] The location of the TIPS group within this product was established using COSY experiments. Upon treating compound **29** with methyl iodide in the presence of sodium hydride, *bis*-ether **30** (49%) rather than the anticipated regioisomer was obtained. Because the illustrated locations of the ether residues within compound **30** (that thwart the application of the anticipated Eschenmoser–Claisen rearrangement) were not appreciated until an X-ray analysis was carried out on a derivative, this was carried forward by first treating it with TBAF and thus affording homoallylic alcohol **31** (98%). Compound **31** was engaged in a Suzuki–Miyaura cross-coupling reaction with ester **27** to give

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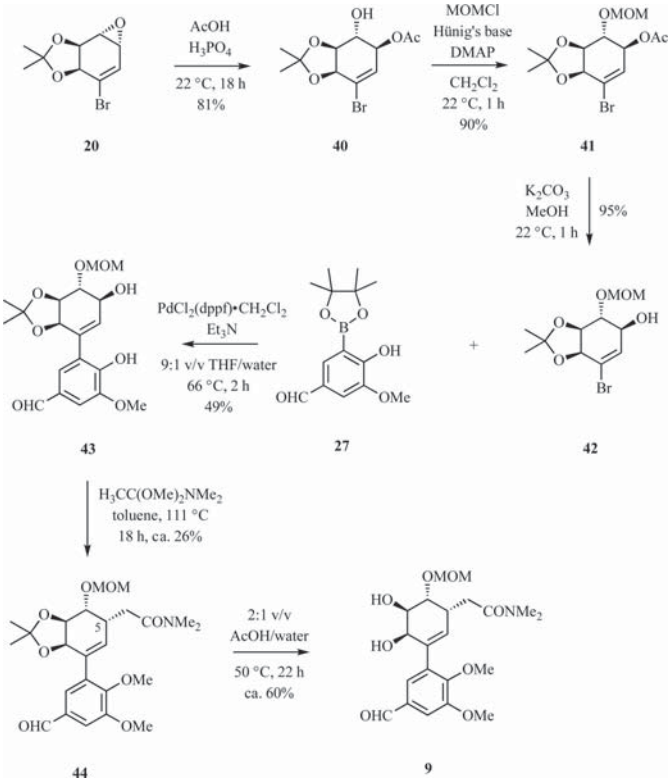
Scheme 9. Synthesis of Analogue 9



the arylated and crystalline cyclohexene **32** (45%), the illustrated structure of which was established by single-crystal X-ray analysis. Acid-catalyzed hydrolysis of the acetonide residue within the last compound then gave triol **33** (81%). Even though the position of the methoxy group within compound **33** precluded the application of the type of EC rearrangement used earlier, it was subjected to an intramolecular Mitsunobu reaction so as to produce a system, namely compound **7** (85%), that embodies the ABC-ring ensemble associated with (−)-galanthamine.

The synthesis of analogue **8** is shown in Scheme 8 and involved, as the initial step, the regio- and diastereo-selective *cis*-dihydroxylation of diene **19**. Selective silylation of the allylic hydroxyl group within the resulting and previously reported[17b,31] diol **34** (62%) was readily achieved using TIPS-OTf in the presence of 2,6-lutidine, and the product ether **35** (88%) was subjected to *O*-methylation using methyl iodide/base.

Treatment of product *bis*-ether **36** (92%) with TBAF resulted in cleavage of the *O*-TIPS bond and formation of alcohol **37** (88%) that could be cross-coupled with boronate ester **27** under Suzuki−Miyaura conditions and thus affording the anticipated product **38** (55%). Contrary to expectations, however, the allylic alcohol residue within compound **38** failed to engage in an Eschenmoser−Claisen rearrangement upon treatment with *N*,*N*-dimethylacetamide dimethyl acetal. Rather, the replacement of the associated allylic hydroxyl group with an *N*,*N*-dimethylacetamide residue took place to give, in a stereoselective manner and after accompanying *O*-methylation of the phenolic hydroxyl group, amide **39** (40%). This was contaminated by small amounts (7%) of its chromatographically inseparable C5 epimer. "Thwarted E-C rearrangements" of this type have been reported previously[32] and in this instance the process may be driven by electron-rich arene residues facilitating ionization of the intermediate mixed acetal with the ensuing and extensively stabilized cation then undergoing nucleophilic capture by 1-methoxy-*N*,*N*-dimethylethen-1-amine that is itself generated through thermal cracking of the starting dimethyl acetal. The basic structure of product **39** follows from the observation that the diastereotopic methylene hydrogens of the acetamide side-chain both show vicinal couplings to the adjacent allylic hydrogen. The illustrated configuration of the C5 acetamide residue is assigned on the basis that this would be introduced preferentially during the course of the nucleophilic capture process mentioned above from that face of the intermediate cation opposite to the sterically demanding and nearby acetonide residue. Hydrolysis of this acetonide residue within compound **33** under standard conditions then gave analogue **8** in 69% yield.

The synthesis of final galanthamine analogue **9** followed a very similar route to that used in preparing congener **8**. The reaction sequence involved is shown in Scheme 9. Thus, reaction of epoxide **19** with acetic acid in the presence of a mineral acid gave the previously reported *trans*-diol monoacetate **40**[9a] (81%), the free hydroxyl of which was protected as

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the corresponding MOM ether using standard protocols and thus affording compound **41**[9a] in 90% yield.

Cleavage of the acetate unit with the last compound could be effected under conventional conditions, and the resulting allylic alcohol **42**[9a] (95%) then cross-coupled with boronate ester **27** in the usual manner to give product **43** (49%). As was the case with congener **32** (Scheme 8), upon subjecting compound **43** to conditions often used to effect the EC rearrangement, this substrate also engaged in both an allylic substitution reaction and *O*-methylation of the phenolic hydroxyl of the precursor. As a consequence, a chromatographically inseparable and 3:1 mixture of amide **44** and its β-epimer (35% combined yield) was formed. The salient spectral features of compound **44** resembled those of congener **33**. Hydrolysis of the mixture of acetonide **44** and its C5-epimer under conventional conditions then gave, after chromatographic purification, diol **9** (69%) that, like the other galanthamine derivatives/analogues, was subjected to molecular docking studies and evaluation as a potential inhibitor of acetylcholine esterase. Details are presented in the following section.

Biological Evaluation and Molecular Docking Studies. The above-mentioned derivatives/analogues of (−)- and (+)-galanthamine were each evaluated for their ability to inhibit AChE using a modified method involving addition of DMSO so as to ensure dissolution of these otherwise rather insoluble compounds.[33] The inhibitory effect of DMSO itself on the AChE was taken into account by subtracting a control measurement for obtaining the IC_{50} values of the tested materials. A summary of the inhibition data thus obtained is shown in Table 1. These assays reveal that only one of the

Table 1. Outcomes of Evaluating Galanthamine Derivatives and Analogues as Inhibitors of AChE and Their Calculated Docking Binding Energies (BEs)

entry	compd	IC_{50} (μM)	docking BE (kcal)
1	**2**	>500	−8.9
2	*ent*-**2**	>500	−9.6
3	**3**	420 ± 57	−8.4
4	*ent*-**3**	>500	−9.5
5	**4**	>500	−6.0
6	*ent*-**4**	>500	−9.1
7	**5**	>500	
8	*ent*-**5**	>500	
9	**6**	>500	−6.3
10	*ent*-**6**	>500	−9.2
11	**7**	>500	−7.8
12	**8**	>500	
13	**9**	>500	
14	**1** (+ve control)	0.9 ± 0.2	−10.2

compounds, namely derivative **3**, showed a measurable IC_{50} value (of 420 μM) compared to the positive control (−)-galanthamine [(−)-**1**] which had an IC_{50} value of 0.9 μM. Clearly, then, and regardless of the absolute stereochemistries of the systems involved, none of the above-mentioned derivatives/analogues are strong inhibitors of AChE.

Analysis of these inhibition data was undertaken through molecular docking simulations and using the structure of (−)-galanthamine bound to human AChE.[34] Crystallographic studies have revealed that (−)-galanthamine binds into the active site of AChE with the tetrahydroazepine or D-ring assuming a boat-like conformation and the associated *N*-methyl group in a pseudoequatorial orientation spanning the acyl- and choline-binding sites.[35] Docking simulations, using AUTODOCK, matched the solved structure (see Figure 4A) with the

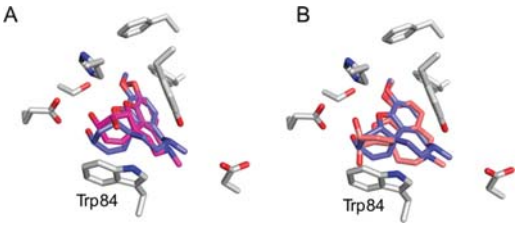

Figure 4. Overlap of (−)-galanthamine (**1**) (blue) and the docked derivatives **3** (**A**, purple) and *ent*-**3** (**B**, peach) in the active site of AChE.

key interactions between AChE and (−)-galanthamine being evident, thus suggesting that docking simulations of this type can provide the correct orientation of binding for the compounds. Surprisingly, with the exception of compounds **5** and *ent*-**5**, **8** and **9**, for which no bound structures could be obtained (in the case of the first two of these compounds, this may be a consequence of their significantly greater size), the derivatives all had significant docking binding energies, albeit weaker than (−)-galanthamine (see right-hand column, Table 1). This highlights some of the known limitations in the prediction of binding affinity by docking programs.[36−38] The docking studies do, however, reveal the likely structural basis for the reduced affinity of these analogues. For example, the configuration of compound **3** matches the orientation of (−)-galanthamine, except that the additional (C5) hydroxyl moiety is positioned toward tryptophan 84 and thus produces a distortion in the shape of the A-ring. This most likely results in destabilization of the $\pi-\pi$ stacking interaction between the indole ring of Trp84 and this ring (A)[39] with this loss of interaction impairing the compound's capacity to inhibit AChE.

The (+)-enantiomer, *ent*-**3**, of compound **3** also has a hydroxyl positioned toward Trp84, again disrupting the stabilizing cyclohexene−indole interactions, although on this occasion it is the same hydroxyl moiety that is present in galanthamine, potentially explaining, in part at least, why (+)-galanthamine derivatives are not potent inhibitors of AChE.

■ CONCLUSIONS

The synthetic chemistry studies detailed above have established that the ABC-ring system of galanthamine is readily obtained through the Suzuki−Miyaura cross-coupling of *o*-hydroxyarylboronates with conduritols incorporating a brominated double-bond and then engaging the products of such processes in an intramolecular Mitsunobu reaction. Furthermore, most of the polyhydroxylated tetrahydrodibenzofurans arising from such a reaction sequence engage in a thermally promoted Eschenmoser−Claisen-type rearrangement reaction upon treatment with *N*,*N*-dimethylacetamide dimethyl acetal in refluxing toluene. The angularly substituted tetrahydrodibenzofurans thus formed, which embody the quaternary carbon center associated with the title alkaloid and represent monoseco analogues of the same, can then be elaborated, using Pictet−Spengler chemistry, to give oxygenated derivatives of galanthamine, certain variants of which have recently been isolated

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from Chinese medicinal plants.[40] Interestingly, these new natural products were also poor inhibitors of AChE.

The biological evaluation of the galanthamine derivatives and analogues obtained by the pathways described above reveals the finely tuned nature of the interactions of the parent alkaloid with the target enzyme AChE. In particular, structurally "modest" changes to the galanthamine framework, as embodied in the oxygenated derivatives **2**, *ent*-**2**, **3**, and *ent*-**3**, can completely disrupt binding such that the compounds are rendered inactive. These studies have also revealed that the computational prediction of the likely binding affinity of galanthamine analogues to AChE is fraught.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on an FTIR spectrometer. Samples were analyzed as thin films or finely divided solids. Low-resolution ESI mass spectra were recorded on a single quadrupole mass spectrometer interfaced with a liquid chromatograph, whereas high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid:ceric sulfate:sulfuric acid (concd):water (37.5 g: 7.5 g: 37.5 g: 720 mL), potassium permanganate:potassium carbonate:5% w/v aq. sodium hydroxide solution:water (3 g: 20 g: 5 mL: 300 mL)), *p*-anisaldehyde or vanillin:sulfuric acid (concd):ethanol (15 g: 2.5 mL: 250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[41] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and used as supplied. THF, methanol, and CH_2Cl_2 were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[42]

*Specific Chemical Transformations (2R,3R,4aS,5S,8R,8aS)-6-(2-Hydroxy-3-methoxy-phenyl)-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[b][1,4]dioxine-5,8-di -ol (**13**) and Enantiomer ent-**13**.* A magnetically stirred solution of *bis*-acetal **11**[15] (805 mg, 2.37 mmol), ester **12** (720 mg, 2.88 mmol), and triethylamine (3 mL) in THF/water (20 mL of a 9:1 v/v mixture) was subjected to sonication under an atmosphere of nitrogen for 0.5 h. $PdCl_2$dppf·CH_2Cl_2 (140 mg, 0.191 mmol) was then added, and the ensuing mixture was heated under reflux for 2 h before being cooled and quenched with phosphate buffer (5 mL of a 1 M aqueous solution at pH 7). The mixture thus obtained was cooled to 0 °C, treated with methanol/30% aq hydrogen peroxide (10 mL of a 1:1 v/v mixture), and then allowed to warm to room temperature over 1 h. The resulting mixture was diluted with water (50 mL) and extracted with ethyl acetate (5 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing thick orange oil was triturated with diethyl ether (5 × 2 mL), and the resulting yellow solid was subjected to flash column chromatography (silica, 4:15:1 v/v ethyl acetate/hexane/methanol →12:7:1 v/v ethyl acetate/hexane/methanol gradient elution). Concentration of the appropriate fractions (R_f = 0.3 in 10:9:1 v/v/v ethyl acetate/hexane/methanol) afforded phenol **13** (618 mg, 68%) as a white powder: mp 202−210 °C; $[\alpha]^{20}_D$ −93.8 (*c* 0.1, methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 6.89 (dd, J = 7.5 and 1.8 Hz, 1H), 6.83−6.73 (complex m, 2H), 5.76 (d, J = 2.5 Hz, 1H), 4.60 (d, J = 3.7 Hz, 1H), 4.23 (dd, J = 8.0 and 2.5 Hz, 1H), 4.09 (dd, J = 11.0 and 8.0 Hz, 1H), 3.85 (s, 3H), 3.69 (dd, J = 11.0 and 3.7 Hz, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H) (signals due to hydroxyl protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 149.0, 145.0, 138.9, 132.9, 128.6, 123.6, 120.3, 112.2, 100.7, 100.3, 71.4, 70.7, 69.7, 69.0, 56.6, 48.3, 48.2, 18.1(5), 18.1(0); IR ν_{max} 3456, 3283, 2941, 1589, 1468, 1218, 1129, 1119, 914, 594 cm^{-1}; MS (ESI, +ve) m/z 788 ([(2 M + Na)$^+$, 80%], 405 [(M + Na)$^+$, 100]; HRMS (ESI, +ve) m/z (M + Na)$^+$ calcd for $C_{19}H_{26}NaO_8$ 405.1525, found 405.1526.

Compound *ent*-**13** was prepared in an analogous fashion from *ent*-**11** (2.04 g, 5.34 mmol) to give 1.60 g (71%) of product; $[\alpha]^{20}_D$ +86.4 (*c* 0.1, methanol). All of the other spectral data acquired on this material were identical with those reported above for compound **13**.

*(2R,3R,4aS,5R,11aR,11bS)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,4a,5,11a,11b-hexahydrobenzo[b][1,4]dioxino[2,3-g]-benzofuran-5-ol (**14**) and Enantiomer ent-**14**.* A magnetically stirred solution of phenol **13** (605 mg, 1.58 mmol) and PPh_3 (456 mg, 1.74 mmol) in THF (70 mL) maintained at −5 °C was treated dropwise over 0.5 h with di-*iso*-propyl azodicarboxylate (364 μL, 1.74 mmol). The resulting solution was stirred at −5 °C for 4 h and then allowed to warm to room temperature over 1 h before being concentrated under reduced pressure. The orange oil thus obtained was subjected to two successive flash chromatographic separations (silica, hexane → 1:1 v/v ethyl acetate/hexane gradient elution), and concentration of appropriate fractions (R_f = 0.7, 2:1 v/v ethyl acetate/hexane) afforded allylic alcohol **14** (193 mg, 33%) as a white foam; $[\alpha]^{20}_D$ −157 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 7.5 and 1.2 Hz, 1H), 6.89 (apparent t, J = 7.5 Hz, 1H), 6.82 (dd, J = 8.1 and 1.2 Hz, 1H), 5.81 (m, 1H), 5.14 (dt, J = 9.0 and 3.6 Hz, 1H), 4.67−4.61 (complex m, 1H), 4.04 (dd, J = 10.5 and 9.0 Hz, 1H), 3.93 (dd, J = 10.5 and 7.7 Hz, 1H), 3.88 (s, 3H), 3.34 (s, 6H), 2.34 (d, J = 4.8 Hz, 1H), 1.36(3) (s, 3H), 1.35(9) (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 145.4, 139.1, 125.7, 122.1, 116.2, 113.6, 113.5, 99.2, 98.9, 84.0, 74.1, 71.3, 70.1, 56.0, 48.4, 48.0, 17.7, 17.6; IR ν_{max} 3486, 2959, 2897, 1614, 1597, 1494, 1445, 1133, 1114, 1098, 1035, 1015, 786 cm^{-1}; MS (ESI, +ve) m/z 752 [(2 M + Na)$^+$, 25%], 387 [(M + Na)$^+$, 100%]; HRMS (ESI, +ve) m/z (M + Na)$^+$ calcd for $C_{19}H_{24}NaO_7$ 387.1420, found 387.1423.

Compound *ent*-**14** was prepared in an analogous fashion from *ent*-**13** (345 mg, 0.90 mmol) to give 314 mg (96%) of product; $[\alpha]^{20}_D$ +102 (*c* 1.0, $CHCl_3$). All the other spectral data acquired on this material were identical with those reported above for compound **14**.

*N,N-Dimethyl-2-((2R,3R,4aS,6aS,11aR,11bR)-2,3,10-trimethoxy-2,3-dimethyl-2,3,11a,11b-tetrahydrobenzo[b][1,4]dioxino[2,3-g]-benzofuran-6a(4aH)-yl)acetamide (**15**) and Enantiomer ent-**15**.* A magnetically stirred solution of allylic alcohol **14** (180 mg, 0.494 mmol) in toluene (20 mL) maintained at 22 °C was treated with *N,N*-dimethylacetamide dimethyl acetal (900 μL, 4.9 mmol), and the resulting solution was heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue thus obtained was triturated with diethyl ether. The resulting waxy solid was subjected to flash chromatography (silica, 20:79:1 v/v ethyl acetate/hexane/methanol → 60:39:1 v/v ethyl acetate/hexane/methanol gradient elution), and concentration of appropriate fractions (R_f = 0.2 in 2:1 v/v ethyl acetate/hexane) afforded amide **15** (178 mg 84%) as a white foam; $[\alpha]^{20}_D$ −89.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (m, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.02 (dd, J = 10.0 and 2.7 Hz, 1H), 5.74 (dd, J = 10.0 and 2.0 Hz, 1H), 5.04 (d, J = 9.6 Hz, 1H), 4.55 (dt, J = 9.6 and 2.0 Hz, 1H), 3.85 (s, 3H), 3.76 (t, J = 9.6 Hz, 1H), 3.30 (s, 3H), 3.16 (s, 3H), 2.89 (s, 3H), 2.78 (s, 3H), 2.71 (d, J = 15.8 Hz, 1H), 2.61 (d, J = 15.8 Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

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169.0, 145.6(4), 145.5(6), 134.2, 128.9, 126.9, 121.5, 115.3, 112.0, 99.8, 87.1, 70.5, 65.9, 56.1, 51.0, 48.1, 47.4, 42.5, 37.3, 35.3, 17.7(4), 17.7(0) (one signal obscured or overlapping); IR ν_{max} 2954, 2889, 1651, 1491, 1459, 1380, 1276, 1115, 1061, 1000, 954, 739 cm^{-1}; MS (ESI, +ve) m/z 456 [$(M + Na)^+$, 100%], 201 (35); HRMS (ESI, +ve) m/z $(M + Na)^+$ calcd for $C_{23}H_{31}NNaO_7$ 456.1998, found 456.2000.

Compound *ent*-**15** was prepared in an analogous fashion from *ent*-**14** (234 mg, 0.64 mmol) to give 238 mg (86%) of product as a white foam. A small sample was crystallized (diethyl ether/methanol/hexane) to give a white, crystalline solid; mp 160−165 °C (dec); $[\alpha]^{20}_D$ +87.1 (*c* 1.0, $CHCl_3$). All of the other spectral data acquired on this material were identical with those reported above for compound **15**.

*2-((2R,3R,4aS,6aS,11aR,11bR)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,11a,11b-tetrahydrobenzo[b][1,4]dioxino[2,3-g]benzofuran-6a-(4aH)-yl)ethan-1-ol (**16**) and Enantiomer ent-**16**.* A magnetically stirred solution of amide **15** (146 mg, 0.337 mmol) in THF (17 mL) maintained at 0 °C was treated dropwise with lithium triethylborohydride (1.7 mL of a 1 M solution in THF, 1.7 mmol). The resulting mixture was warmed to room temperature over 2 h, recooled to 0 °C, quenched with methanol (2 mL), and then treated with silica (200 mg of flash chromatographic-grade material) before being subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane → 1:1 v/v ethyl acetate/hexane gradient elution). Concentration of relevant fractions (R_f = 0.6, 2:1 v/v ethyl acetate/hexane) afforded compound **16** (122 mg, 92%) as a white foam; $[\alpha]^{20}_D$ −131.9 (*c* 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (apparent t, *J* = 7.8 Hz, 1H), 6.74 (m, 1H), 6.69 (dd, *J* = 7.5 and 1.2 Hz, 1H), 5.91 (broad d, *J* = 10.0 Hz, 1H), 5.70 (broad d, *J* = 10.0 Hz, 1H), 4.89 (d, *J* = 9.6 Hz, 1H), 4.31 (ddd, *J* = 9.6, 2.7, and 1.5 Hz, 1H), 3.84 (s, 3H), 3.72 (t, *J* = 9.6 Hz, 1H), 3.67−3.57 (complex m, 2H), 3.28 (s, 3H), 3.17 (s, 3H), 1.96 (dt, *J* = 13.7 and 6.7 Hz, 1H), 1.85 (dt, *J* = 13.7 and 6.4 Hz, 1H), 1.40 (triplet, *J* = 5.2 Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 145.4, 133.6, 130.1, 126.4, 121.8, 114.9, 112.0, 99.9, 99.7, 86.9, 70.8, 65.4, 59.3, 56.1, 51.7, 48.0, 47.5, 43.5, 17.7, 17.6; IR ν_{max} 3508, 2948, 2837, 1619, 1588, 1491, 1459, 1281, 1130, 1116, 1036, 753, 736 cm^{-1}; MS (ESI, +ve) m/z 415 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) m/z $(M + Na)^+$ calcd for $C_{21}H_{28}NaO_7$ 415.1733, found 415.1733.

Compound *ent*-**16** was prepared in an analogous fashion from *ent*-**15** (177 mg, 0.408 mmol) to give 160 mg (quantitative) of product; $[\alpha]^{20}_D$ +108 (*c* 0.9, $CHCl_3$). All of the other spectral data acquired on this material were identical with those reported above for compound **16**.

*2-((2R,3R,4aS,6aS,11aR,11bR)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,11a,11b-tetrahydrobenzo[b][1,4]dioxino[2,3-g]benzofuran-6a-(4aH)-yl)acetic Acid (**17**) and Enantiomer ent-**17**.* A magnetically stirred solution of alcohol **16** (122 mg, 0.310 mmol) in acetonitrile/water (9:1 v/v, 2.3 mL) maintained at room temperature was treated in one portion with 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate (280 mg, 0.93 mmol). The resulting dark-brown solution was stirred at 22 °C for 48 h (by which time it was a pale-yellow color) and then poured into water (3 mL) and extracted with diethyl ether (5 × 4 mL). The combined organic extracts were washed with HCl (2 × 1 mL of a 1 M aqueous solution) and brine (2 × 5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, CH_2Cl_2 → 1:19 v/v methanol/CH_2Cl_2 gradient elution) and concentration of appropriate fractions (R_f = 0.2 in 1:19 v/v methanol/CH_2Cl_2) afforded acid **17** (96 mg, 76%) as a clear, colorless gum; $[\alpha]^{20}_D$ −88.5 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (m, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 7.4 Hz, 1H), 5.96 (dd, *J* = 10.0 and 2.6 Hz, 1H), 5.77 (d, *J* = 10.0 Hz, 1H), 5.17 (d, *J* = 9.7 Hz, 1H), 4.40 (d, *J* = 9.7 Hz, 1H), 3.85 (s, 3H), 3.75 (t, *J* = 9.7 Hz, 1H), 3.29 (s, 3H), 3.17 (s, 3H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.63 (d, *J* = 15.6 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H) (signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 145.6, 132.9, 128.1, 127.9, 121.9, 115.0, 112.3, 99.9, 99.8, 86.0, 70.5, 65.5, 56.1, 50.9, 48.0, 47.5, 44.0, 17.7 (signals due to two carbons obscured or overlapping); IR ν_{max} 2950, 1710, 1712, 1619, 1491, 1459, 1284, 1128, 1116, 1034, 960, 732 cm^{-1}; MS (ESI, +ve) m/z 429 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) m/z $(M + Na)^+$ calcd for $C_{21}H_{26}NaO_8$ 429.1525, found 429.1524.

Compound *ent*-**17** was prepared in an analogous fashion from *ent*-**16** (150 mg, 0.382 mmol) to give 115 mg (80%) of product; $[\alpha]^{20}_D$ +95.7 (*c* 1.2, $CHCl_3$). All of the other spectral data acquired on this material were identical with those reported above for compound **17**.

*N-Methyl-2-((2R,3R,4aS,6aS,11aR,11bR)-2,3,10-trimethoxy-2,3-dimethyl-2,3,-11a,11b-tetrahydrobenzo[b][1,4]dioxino[2,3-g]-benzofuran-6a(4aH)-yl)acetamide (**5**) and Enantiomer ent-**5**.* A magnetically stirred solution of acid **17** (93 mg, 0.23 mmol) in THF (12 mL) maintained at room temperature was treated with 1,1′-carbonyldiimidazole (49 mg, 0.30 mmol). The resulting solution was heated under reflux for 1 h before being cooled to room temperature and then placed in an ice bath at 0 °C. Methylamine (700 μL of a 2 M solution in THF, 1.4 mmol) was then added dropwise, and the ensuing solution was maintained at 0 °C for 3 h before being warmed to 22 °C and stirred at this temperature for another 8 h. After this time, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with NH_4Cl (3 × 15 mL of a saturated aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were washed with brine (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:15:1 v/v ethyl acetate/hexane/methanol → 8:11:1 v/v ethyl acetate/hexane/methanol gradient elution) and concentration of appropriate fractions (R_f = 0.3 in 10:9:1 v/v ethyl acetate/hexane/methanol) gave amide **5** (76 mg, 79%) as a clear, colorless oil; $[\alpha]^{20}_D$ −102.1 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (m, 1H), 6.72 (dd, *J* = 8.0 and 1.2 Hz, 1H), 6.68 (dd, *J* = 7.5 and 1.2 Hz, 1H), 6.09 (dd, *J* = 10.0 and 2.6 Hz, 1H), 5.72 (dd, *J* = 10.0 and 1.5 Hz, 1H), 5.36 (broad q, *J* = 4.8 Hz, 1H), 4.97 (d, *J* = 9.7 Hz, 1H), 4.37 (ddd, *J* = 9.7, 2.6, and 1.5 Hz, 1H), 3.81 (s, 3H), 3.71 (t, *J* = 9.7 Hz, 1H), 3.27 (s, 3H), 3.13 (s, 3H), 2.71 (d, *J* = 4.8 Hz, 3H), 2.51 (d, *J* = 14.0 Hz, 1H), 2.42 (d, *J* = 14.0 Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 145.5, 133.4, 128.7, 126.9, 121.6, 115.2, 112.1, 99.8, 99.7, 86.9, 70.3, 65.5, 56.0, 51.2, 48.0, 47.4, 46.8, 26.2, 17.7, 17.6 (signal due to one carbon obscured or overlapping); IR ν_{max} 3317, 2952, 2921, 1646, 1548, 1491, 1457, 1377, 1197, 1114, 1034, 999, 955, 735 cm^{-1}; MS (ESI, +ve) m/z 442 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) m/z $(M + Na)^+$ calcd for $C_{22}H_{29}NNaO_7$ 442.1842, found 442.1842.

Compound *ent*-**5** was prepared in an analogous fashion from *ent*-**17** (115 mg, 0.28 mmol) to give 91 mg (79%) of product; $[\alpha]^{20}_D$ +89.1 (*c* 1.3, $CHCl_3$). All of the other spectral data acquired on this material were identical with those reported above for compound **5**.

*2-((5aR,6R,7S,9aS)-6,7-Dihydroxy-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)-N-methylacetamide (**6**) and Enantiomer ent-**6**.* A round-bottomed flask charged with a magnetic stirrer bar and amide **5** (16.7 mg, 0.04 mmol) was treated sequentially with water (250 μL) and trifluoroacetic acid (250 μL) and the ensuing mixture stirred at 22 °C for 0.5 h; then, the volatiles were removed under reduced pressure. The residue thus obtained was subject to flash chromatography (silica, 5:4:1 v/v ethyl acetate/hexane/methanol) and concentration of appropriate fractions (R_f = 0.3 in 8:1:1 v/v ethyl acetate/hexane/methanol) afforded diol **6** (8.1 mg, 66%) as a white foam; $[\alpha]^{20}_D$ −11 (*c* 0.4, methanol); ^1H NMR [400 MHz, $(CD_3)_2CO$] δ 7.04 (broad s, 1H), 6.84−6.74 (complex m, 3H), 6.00 (dd, *J* = 10.1 and 2.3 Hz, 1H), 5.67 (dd, *J* = 10.1 and 1.5 Hz, 1H), 5.25 (d, *J* = 8.7 Hz, 1H), 4.75 (broad s, 1H), 4.22 (partially obscured and broad s, 1H), 4.18 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.40 (t, *J* = 8.7 Hz, 1H), 2.63 (d, *J* = 4.6 Hz, 3H), 2.48 (d, *J* = 13.9 Hz, 1H), 2.41 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 170.7, 146.9, 146.2, 135.5, 131.6, 128.5, 122.1, 116.1, 113.3, 90.4, 75.8, 69.9, 56.4, 51.6, 46.8, 25.9; IR ν_{max} 3315, 2943, 1642, 1491, 1272, 1199, 1179, 1132, 1064, 945, 723 cm^{-1}; MS (ESI, +ve) m/z 634 [$(2\ M + Na)^+$, 40], 328 [$(M + Na)^+$, 100]; HRMS (ESI, +ve) m/z $(M + Na)^+$ calcd for $C_{16}H_{19}NNaO_5$ 328.1161, found 328.1158.

Compound *ent*-**6** was prepared in an analogous fashion from *ent*-**5** (16.7 mg, 0.04 mmol) to give 11.8 mg (97%) of product; $[\alpha]^{20}_D$ +16.7

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(*c* 1.0, methanol). All of the other spectral data acquired on this material were identical with those reported above for compound **6**.

*(4aR,5R,6S,8aS)-5,6-Dihydroxy-3-methoxy-11-methyl-4a,5,11,12-tetrahydro-6H-benzo[2,3]benzofuro[4,3-cd]azepin-10(9H)-one (**2**) and Enantiomer ent-**2**.* A magnetically stirred solution of amide **5** (56 mg, 0.133 mmol) in acetonitrile (14 mL) was treated sequentially with paraformaldehyde (20 mg, 0.67 mmol) and trifluoroacetic acid (63 μL, 0.82 mmol). The resulting solution was stirred at room temperature for 8 h and then quenched with phosphate buffer (15 mL of a 1 M aqueous solution at pH 7) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (1 × 5 mL) and dried (Na_2SO_4) before being filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:15:1 v/v ethyl acetate/hexane/methanol → 8:1:1 v/v ethyl acetate/hexane/methanol gradient elution) and concentration of the appropriate fractions (R_f = 0.4 in 8:1:1 v/v ethyl acetate/hexane/methanol) afforded lactam **2** (19.7 mg, 47%) as a white, amorphous solid; $[\alpha]^{20}_D$ −139 (*c* 0.4, methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (apparent s, 2H), 5.97 (dd, *J* = 10.2 and 4.7 Hz, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.78−4.73 (complex m, 1H), 4.67−4.63 (complex m, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 4.12 (m, 1H), 3.85 (s, 3H), 3.18 (d, *J* = 14.2 Hz, 1H), 3.07 (d, *J* = 14.2 Hz, 1H), 3.04 (s, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 145.9, 144.8, 131.9, 128.7, 125.7, 125.1, 120.4, 111.9, 88.4, 68.5, 67.0, 56.1, 52.1, 43.2, 42.3, 35.9; IR ν_{max} 3357, 2924, 1623, 1508, 1438, 1280, 1101, 1070, 1031, 971, 880, 793 cm^{-1}; MS (ESI, +ve) *m*/*z* 657 [(2 M + Na)$^+$, 40%], 340 [(M + Na)$^+$, 100]; HRMS (ESI, +ve) *m*/*z* (M + Na)$^+$ calcd for $C_{17}H_{19}NNaO_5$ 340.1161, found 340.1159.

Compound *ent*-**2** was prepared in an analogous fashion from *ent*-**5** (20 mg, 0.048 mmol) to give 9.5 mg (63%) of product as a white, amorphous solid. A small sample was recrystallized (diethyl ether) to give a white, crystalline solid; mp 135−140 °C; $[\alpha]^{20}_D$ +127 (*c* 0.4, methanol). All of the other spectral data acquired on this material were identical with those reported above for compound **2**.

*(4aR,5R,6S,8aS)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzo[2,3]-benzofuro[4,3-cd]azepine-5,6-diol (**3**) and Enantiomer ent-**3**.* A magnetically stirred solution of lactam **2** (9.5 mg, 0.03 mmol) in THF (5 mL) maintained at room temperature was treated with $NaAlH_2(OCH_2CH_2OCH_3)_2$ (60 μL of a 60% w/v solution in toluene, 0.184 mmol) and the ensuing mixture heated under reflux for 24 h after which time it was cooled to 0 °C (ice-bath), quenched with potassium sodium tartrate (2 mL of a saturated aqueous solution), diluted with water (10 mL) and then extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were washed with brine (1 × 2 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:19 v/v NH_3 saturated methanol/$CHCl_3$ → 1:9 v/v NH_3 saturated methanol/$CHCl_3$ gradient elution) and concentration of appropriate fractions (R_f = 0.2 in 1:9 v/v NH_3 saturated methanol/$CHCl_3$) afforded amine **3** (4.0 mg, 44%) as a white, amorphous solid; $[\alpha]^{20}_D$ −86.6 (*c* 0.3, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.23 (d, *J* = 10.2 Hz, 1H), 5.93 (dd, *J* = 10.2 and 3.8 Hz, 1H), 4.57 (d, *J* = 4.6 Hz, 1H), 4.30 (m, 1H), 4.19−4.09 (complex m, 2H), 3.84 (s, 3H), 3.63 (m, 1H), 3.27 (m, 1H), 2.98 (broad d, *J* = 14.8 Hz, 1H), 2.34 (s, 3H), 2.18 (m, 1H), 1.81 (dd, *J* = 13.4 and 2.2 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.0, 132.3, 129.1, 128.1, 126.6, 122.4, 111.1, 90.9, 72.4, 67.6, 60.1, 55.9, 54.2, 49.8, 42.0, 36.0; IR ν_{max} 3345, 2921, 1626, 1596, 1507, 1439, 1282, 1041, 948, 793, 726 cm^{-1}; MS (ESI, +ve) *m*/*z* 629 [(2 M + Na)$^+$, 30%], 326 [(M + Na)$^+$, 100], 304 [(M + H)$^+$, 7]; HRMS (ESI, +ve) *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{22}NO_4$ 304.1549, found 304.1544.

Compound *ent*-**3** was prepared in an analogous fashion from *ent*-**2** (9.5 mg, 0.030 mmol) to give 4.0 mg (44%) of product, $[\alpha]^{20}_D$ +60.5 (*c* 0.4, $CDCl_3$). All of the other spectral data acquired on this material were identical with those reported above for compound **3**.

*2-((5aR,6R,7S,9aS)-6,7-Dihydroxy-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a-(5aH)-yl)-N,N-dimethylacetamide (**4**) and Enantiomer ent-**4**.* Amide **15** (15 mg, 0.035 mmol) was treated trifluoroacetic acid/water (200 μL of a 1:1 v/v mixture), and the resulting mixture was stirred at 22 °C for 0.5 h; then, the volatiles were removed under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:19 v/v methanol/CH_2Cl_2), and concentration of the relevant fractions (R_f = 0.1) afforded diol **4** (9.8 mg, 88%) as a clear, colorless oil; $[\alpha]^{20}_D$ +5.7 (*c* 0.9, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (m, 1H), 6.78−6.73 (complex m, 2H), 5.98 (d, *J* = 9.9 Hz, 1H), 5.83 (d, *J* = 9.9 Hz, 1H), 5.01 (d, *J* = 7.5 Hz, 1H), 4.45 (broad s, 1H), 3.85 (s, 3H), 3.71 (m, 1H), 2.88 (s, 3H), 2.81 (s, 3H), 2.79 (m, 1H), 2.58 (d, *J* = 15.8 Hz, 1H) (signals due to hydroxyl protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 145.5, 145.3, 134.1, 129.4, 128.5, 122.0, 115.4, 111.9, 90.5, 74.4, 69.2, 56.1, 50.1, 42.7, 37.5, 35.6; IR ν_{max} 3389, 2927, 1616, 1489, 1457, 1402, 1271, 1093, 1058, 941, 749, 731 cm^{-1}; MS (ESI, +ve) *m*/*z* 661 [(2 M + Na)$^+$, 40%], 342 [(M + Na)$^+$, 100]; HRMS (ESI, +ve) *m*/*z* (M + Na)$^+$ calcd for $C_{17}H_{21}NNaO_5$ 342.1317, found 342.1311.

Compound *ent*-**4** was prepared in an analogous fashion from *ent*-**15** (23.7 mg, 0.055 mmol) to give 13.4 mg (77%) of product; $[\alpha]^{20}_D$ −8.2 (*c* 1.3, methanol). All of the other spectral data acquired on this material were identical with those reported above for compound **4**.

*(1S,2S,3S,6S)-4-Bromo-6-((4-methoxybenzyl)oxy)cyclohex-4-ene-1,2,3-triol (**21**). Step i.* $BF_3{\cdot}OEt_2$ (100 μL of a 10% v/v solution in CH_2Cl_2) was added dropwise over 0.25 h to a magnetically stirred solution of epoxide 20[23] (2.00 g, 8.09 mmol) and *p*-methoxybenzyl alcohol (23.8 g, 175 mmol) in dry CH_2Cl_2 (80 mL) maintained at −20 °C. The resulting solution was allowed to warm to −10 °C over 2 h after which time a second aliquot of $BF_3{\cdot}OEt_2$ (150 μL of a 10% v/v solution in CH_2Cl_2) was added dropwise over 0.25 h. The reaction mixture thus formed was warmed to 22 °C over 12 h then quenched with phosphate buffer (3 mL of a 1 M aqueous solution at pH 7), and the solvent was then removed under reduced pressure. The residue thus obtained, which was comprised of a mixture of the desired PMB-ether and *p*-methoxybenzyl alcohol, was submitted directly to step ii as detailed immediately below.

Step ii. A magnetically stirred solution of the material obtained from step i in methanol (160 mL) was treated with pyridinium *p*-toluenesulfonate (2.03 g, 8.09 mmol) and the mixture so-formed was heated at 50 °C for 48 h; then, it was cooled to 22 °C and treated with $NaHCO_3$ (500 mg), and the solvent was removed under reduced pressure. The residue thus obtained was treated with ethyl acetate (200 mL) and then water (100 mL), and the separated aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (1 × 30 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash column chromatography (silica, CH_2Cl_2 → 1:19 v/v methanol/CH_2Cl_2 gradient elution), and concentration of appropriate fractions (R_f = 0.2 in 1:19 v/v methanol/CH_2Cl_2) afforded triol **21** (1.98 g, 71% from **20**) as a white foam; $[\alpha]^{20}_D$ +132.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.14 (d, *J* = 2.4 Hz, 1H), 4.67 (s, 2H), 4.58 (d, *J* = 5.1 Hz, 1H), 4.27−4.20 (complex m, 2H), 4.03 (broad s, 1H), 3.86 (dd, *J* = 7.4 and 2.0 Hz, 1H), 3.82 (broad d, *J* = 9.7 Hz, 1H), 3.78 (s, 3H), 3.54 (m, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 160.2, 132.8, 131.8, 130.2, 124.8, 114.4, 80.8, 74.1, 72.3(2), 72.2(5), 71.8, 55.5; IR (KBr) ν_{max} 3437, 2918, 2848, 1732, 1449, 1368, 1241, 1072, 1026 cm^{-1}; MS (ESI, +ve) *m*/*z* 369 and 367 [(M + Na)$^+$, 100 and 98%]; HRMS (ESI, +ve) *m*/*z* (M + Na)$^+$ calcd for $C_{14}H_{17}{}^{79}BrNaO_5$ 367.0155, found 367.0157.

*(2S,3S,4aR,5S,8S,8aR)-6-Bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[b][1,4]dioxine-5,8-diol (ent-**11**).* A magnetically stirred solution of triol **21** (2.57 g, 7.44 mmol), 2,2,3,3-tetramethoxybutane (1.91 g, 10.7 mmol), and trimethyl orthoformate (3.40 mL, 31.1 mmol) in dry methanol (50 mL) was treated with *p*-TsOH·H_2O (73 mg, 5 mol %). The resulting mixture was heated under reflux for 24 h, cooled to 22 °C, and treated with $NaHCO_3$ (2.00 g), and the solvent was removed under reduced pressure. The residue thus obtained was treated with ethyl acetate (100 mL) and then $NaHCO_3$ (30 mL of a saturated aqueous solution). The separated

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organic phase was washed with $NaHCO_3$ (1 × 30 mL of a saturated aqueous solution) and water (1 × 30 mL), and then the combined aqueous layers were extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (2 × 20 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting thick, orange oil was subjected to flash column chromatography (silica, 1:20 v/v methanol/CH_2Cl_2 elution), and concentration of appropriate fractions (R_f = 0.3) afforded bis-acetal *ent*-**11** (2.14 g, 85%) as a white foam; $[\alpha]^{20}_D$ +72.6 (*c* 1.1, $CHCl_3$) {lit.[15] (for **11**); $[\alpha]^{20}_D$ −76.5 (*c* 1.0, $CHCl_3$)}; ^{1}H NMR (400 MHz, CD_3OD) δ 6.05 (d, *J* = 2.5 Hz, 1H), 4.22 (d, *J* = 4.1 Hz, 1H), 4.06 (dd, *J* = 7.9 and 2.5 Hz, 1H), 3.87 (dd, *J* = 11.1 and 7.9 Hz, 1H), 3.63 (dd, *J* = 11.1 and 4.1 Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 135.2, 124.0, 100.8, 100.2, 73.1, 71.8, 69.8, 69.2, 48.3, 48.2, 18.1, 18.0; IR (KBr) ν_{max} 3160, 2940, 1636, 1454, 1375, 1136, 1077, 1031, 980, 915 cm^{-1}; MS (ESI, +ve) *m*/*z* 363 and 361 [(M + Na)$^+$, 95 and 100%]; HRMS (ESI, +ve) (M+Na)$^+$ calcd for $C_{12}H_{19}{}^{79}BrNaO_6$ 361.0263, found 361.0263.

*3-Bromo-4-hydroxy-5-methoxybenzaldehyde (**23**).* A magnetically stirred solution of vanillin (**22**) (4.00 g, 26.3 mmol) in acetic acid (10 mL) was treated with molecular bromine (1.34 mL, 0.03 mol), and the ensuing mixture was stirred at 22 °C for 3 h during which time a precipitate appeared. The reaction mixture was quenched with water (30 mL), and the precipitate was filtered off, washed with water (1 × 50 mL) and then methanol (1 × 20 mL) before being dried under vacuum to afford compound **23**[28] (5.40 g, 90%) as a white, crystalline solid; mp 164 °C (lit.[28] mp 160−162 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 6.52 (s, 1H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.6, 148.9, 147.7, 130.1, 130.0, 108.2, 108.0, 56.6; IR ν_{max} 3305, 2980, 1674, 1590, 1463, 1290, 1157, 1047, 680 cm^{-1}; MS (ESI, + ev) *m*/*z* 255 and 253 [(M+Na)$^+$, 100 and 99%]; HRMS (ESI, +ve) (M+Na)$^+$ calcd for $C_8H_7{}^{79}BrNaO_3$ 252.9476, found 252.9479.

*2-Bromo-4-(1,3-dioxolan-2-yl)-6-methoxyphenol (**24**).* Compound **23** (5.00 g, 21.8 mmol), toluene (120 mL), *p*-TsOH·H_2O (39 mg, 0.21 mmol) and ethylene glycol (3.60 mL, 65.2 mmol) were placed in a round-bottom flask fitted with a Dean−Stark trap and condenser. The ensuing mixture was heated under reflux for 5 h before being cooled, quenched with $NaHCO_3$ (100 mL of a saturated solution), and extracted with ethyl acetate (1 × 100 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the light-yellow oil thus obtained was subjected flash chromatography (silica, 5:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.4 in 1:9 v/v ethyl acetate/hexane) gave compound **24** (3.30 g, 55%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 1.5 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 5.97 (s, 1H), 5.71 (s, 1H), 4.14−4.11 (complex m, 2H), 4.04−3.98 (complex m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 143.8, 130.7, 123.2, 108.0, 107.9, 102.9, 65.2, 56.4; IR ν_{max} 3358, 2963, 2887, 1684, 1603, 1589, 1503, 1466, 1426, 1280, 1181, 1090, 1044 cm^{-1}; MS (ESI, +ve) *m*/*z* 299 and 297 [(M+Na)$^+$, 92 and 100%] 277 and 275 [(M+H)$^+$, 45 and 40]; HRMS (ESI, +ve) (M+H)$^+$ calcd for $C_{10}H_{12}{}^{79}BrO_4$ 274.9919, found 274.9921.

*2-(3-Bromo-5-methoxy-4-(methoxymethoxy)phenyl)-1,3-dioxolane (**25**).* A magnetically stirred mixture of phenol **24** (3.23 g, 11.79 mmol) in dry THF (30 mL) maintained at 0 °C was treated with NaH (564 mg of a 60% suspension in oil, 14.2 mmol). After 0.5 h, the reaction mixture was treated with chloromethyl methyl ether (980 μL, 12.9 mmol) and then stirred at 22 °C for 18 h before being quenched with water (100 mL; *CAUTION!* possibility of hydrogen gas evolution). The separated aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic phases were washed with brine (1 × 30 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and gave, after concentration of the relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane), bromide **25** (2.65 g, 70%) as a clear, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 5.74 (s, 1H), 5.17 (s, 2H), 4.13−4.01 (complex m, 4H), 3.86 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 143.9, 135.1, 123.1, 117.6, 109.6, 102.6, 98.6, 65.3, 58.0, 56.1; IR ν_{max} 2941, 2891, 2839, 1696, 1570, 1484, 1463, 1416, 1384, 1274, 1157, 1081, 1043, 942, 854 cm^{-1}; MS (EI, 70 eV) *m*/*z* 320 and 318 (M$^{+\bullet}$, 99 and 100%), 289 and 287 (55 and 53), 239 (85), 166 (25); HRMS (EI, 70 eV) M$^{+\bullet}$ calcd for $C_{12}H_{15}{}^{79}BrO_5$ 318.0103, found 318.0104.

*4-Hydroxy-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**27**). Step i.* A magnetically stirred mixture of bromide **25** (1.30 g, 4.15 mmol) in dry THF (15 mL) maintained at −78 °C was treated with *n*-BuLi (3.1 mL of a 1.6 M solution in THF, 5.0 mmol). After 1 h, the reaction mixture was treated with tri-*iso*-propyl borate (1.9 mL, 8.3 mmol) and then stirred at 22 °C for 15 h before being quenched with HCl (10 mL of a 10% w/v aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained, and which is presumed to contain boronic acid **26**, was subjected directly to step ii of the reaction sequence.

Step ii. A magnetically stirred mixture of the product obtained from step i in dry acetonitrile (40 mL) maintained at 0 °C was treated with sodium iodide (0.62 g, 14.5 mmol) and chlorotrimethylsilane (530 μL, 14.5 mmol). The resulting solution was warmed to 22 °C over 4 h and then treated with $Na_2S_2O_3$ (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was immediately subjected to step iii of the reaction sequence.

Step iii. A magnetically stirred suspension of the product obtained from step ii in benzene (30 mL) was treated with pinacol (990 mg, 8.40 mmol), and the solution thus obtained was heated under reflux for 2 h in an apparatus fitted with a Dean−Stark trap and a condenser. The cooled reaction mixture was treated with water (20 mL), and the separated aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:3 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4), boronic ester **27** (520 mg, 45% from **25**) as a white, crystalline solid; mp 73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.33 (s, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 3.93 (s, 3H), 1.38 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.9, 158.6, 148.3, 133.8, 129.6, 111.7, 85.1, 56.0, 24.8; IR ν_{max} 3407, 2992, 2931, 2830, 2797, 2714, 1683, 1620, 1587, 1467, 1388, 1372, 1298, 1256, 1140, 1056, 980, 846, 674 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 (M$^{+\bullet}$, 38%), 221 (100), 178 (51), 177 (30); HRMS (EI, 70 eV) M$^{+\bullet}$ calcd for $C_{14}H_{19}BO_5$ 278.1326, found 278.1326.

*(3aS,4S,5S,7aS)-7-Bromo-2,2-dimethyl-5-((triiso-propylsilyl)oxy)-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol (**29**).* Tri-*iso*-propylsilyl trifluoromethanesulfonate (1.95 mL, 7.3 mmol) was added dropwise to a magnetically stirred solution of compound **28**[29] (1.40 g, 5.3 mmol) and 2,6-lutidine (2.5 mL, 21.5 mmol) in CH_2Cl_2 (30 mL) maintained at −78 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 22 °C over 3 h and then treated with NH_4Cl (60 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (1 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate/hexane elution) and gave, after concentration of the appropriate fractions (R_f = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate/CH_2Cl_2/hexane), an ∼6:1 mixture of compound **29** and its regioisomeric silyl ether (1.95 g, 88% combined yield) as a light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.17 (m, 1H), 4.11 (m, 1H), 3.55 (t, *J* = 8.7 Hz, 1H), 2.45 (s, 1H), 1.54 (s, 3H), 1.40 (s, 3H), 1.15−1.04 (complex m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 110.2, 92.2, 79.3, 77.0, 74.5, 73.6, 28.0, 25.7, 18.0(1), 17.9(9),

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12.4; IR ν_{max} 3469, 2943, 2893, 2866, 1635, 1463, 1382, 1248, 1070, 1019, 997, 882, 866, 828 cm^{-1}; MS (ESI, +ve) m/z 445 and 443 [(M +Na)$^+$, 100 and 97%]; HRMS (ESI, +ve) (M + Na)$^+$ calcd for $C_{18}H_{33}{}^{79}BrNaO_4Si$ 443.1229, found 443.1232.

*(((3aR,4R,5S,7aS)-7-Bromo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]-dioxol-4-yl)oxy)tri-iso-propylsilane (**30**).* Sodium hydride (342 mg of a 60% dispersion in mineral oil, 8.6 mmol) was added to a magnetically stirred solution of an ∼6:1 mixture of compound **29** and its regioisomer (1.20 g, 2.9 mmol) and iodomethane (391 μL, 6.3 mmol) in dry THF (20 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at 22 °C, and then the reaction mixture was treated with ice-water (70 mL) (*CAUTION!* possibility of hydrogen evolution). The separated aqueous phase was extracted with ethyl acetate (1 × 30 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate/CH_2Cl_2/ hexane), an ∼5:1 mixture of compound **30** and its regioisomer (612 mg, 49% combined yield) as a yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major regioisomer) 6.16 (m, 1H), 4.63 (m, 1H), 4.47 (m, 1H), 4.36 (m, 1H), 3.86 (m, 1H), 3.41 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.12−0.95 (complex m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major regioisomer) 129.4, 122.3, 110.0, 77.3, 77.2(3), 77.2(2), 69.9, 57.3, 27.5, 26.2, 18.0(2), 17.9(5), 12.5; IR ν_{max} 2939, 2892, 2866, 1645, 1463, 1381, 1234, 1163, 1078, 1039, 1011, 941, 882, 815, 680 cm^{-1}; MS (ESI, +ve) m/z 459 and 457 [(M+Na)$^+$, 98 and 96%], 355 (100), 347 and 345 (67 and 65); HRMS (ESI, +ve) (M+Na)$^+$ calcd for $C_{19}H_{35}{}^{79}BrNaO_4Si$ 457.1386, found 457.1389.

*(3aS,4R,5S,7aS)-7-Bromo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-[d][1,3]dioxol-4-ol (**31**).* A magnetically stirred solution of an ∼5:1 mixture of compound **30** and its regioisomer (600 mg, 1.4 mmol) in THF (10 mL) maintained at 22 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (2 mL of 1.0 M solution in THF, 2.0 mmol). After 2 h, the reaction mixture was concentrated under reduced pressure, and the residue so-formed was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) to provide, after concentration of the appropriate fractions (R_f = 0.4 in 4:2.5:5.5 v/v/v ethyl acetate/CH_2Cl_2/hexane), compound **31** (377 mg, 98%) as a light-yellow oil; $[\alpha]^{20}_D$ −15.7 (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 1H), 4.68 (d, *J* = 6.5 Hz, 1H), 4.15 (m, 1H), 3.66 (m, 2H), 3.48 (s, 3H), 2.64 (broad s, 1H), 1.55 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 118.8, 111.0, 80.3, 77.5, 77.2, 72.5, 57.5, 28.1, 25.9; IR ν_{max} 3453, 2987, 2934, 2826, 1646, 1457, 1381, 1217, 1164, 1074, 869 cm^{-1}; MS (EI, 70 eV) m/z 280 and 278 (M$^{+\bullet}$, both 3%), 265 and 263 (both 35%), 101 (100); HRMS (EI, 70 eV) M$^{+\bullet}$ calcd for $C_{10}H_{15}{}^{79}BrO_4$ 278.0154, found 278.0148.

*4-Hydroxy-3-((3aR,6S,7R,7aS)-7-hydroxy-6-methoxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-5-methoxybenzaldehyde (**32**).* A magnetically stirred solution of compound **31** (150 mg, 0.54 mmol), ester **27** (180 mg, 0.65 mmol), $PdCl_2$dppf·CH_2Cl_2 (31.5 mg, 0.04 mmol), and triethylamine (3 mL) in THF/water (18 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated under reflux for 2 h before being cooled, poured into water (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane) afforded phenol **32** (85 mg, 45%) as a white, crystalline solid; mp 129 °C, $[\alpha]^{20}_D$ +16.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.39 (d, *J* = 1.8 Hz, 1H), 7.09 (s, 1H), 6.19 (d, *J* = 1.3 Hz, 1H), 5.17 (d, *J* = 6.4 Hz, 1H), 4.27 (dd, *J* = 8.9 and 6.4 Hz, 1H), 3.98 (s, 3H), 3.86 (m, 1H), 3.79 (m, 1H), 3.54 (s, 3H), 2.71 (broad s, 1H), 1.53 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 149.2, 147.7, 132.3, 131.7, 129.2, 128.2, 125.1, 110.7, 108.4, 79.9, 77.7, 73.9, 72.9, 57.5, 56.4, 28.2, 26.0; IR ν_{max} 3400, 2986, 2935, 2830, 1681, 1588, 1488, 1455, 1432, 1373, 1301, 1254, 1217, 1148, 1067, 990, 863, 732 cm^{-1}; MS (EI, 70 eV) m/z 350 (M$^{+\bullet}$, 5%), 292 (53), 260 (55), 232 (100), 231 (72), 218 (53), 203 (39), 189 (33); HRMS (EI, 70 eV) M$^{+\bullet}$ calcd for $C_{18}H_{22}O_7$ 350.1366, found 350.1369.

*(2′R,3′R,4′S,5′S)-2′,3′,4′,6-Tetrahydroxy-5,5′-dimethoxy-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-3-carbaldehyde (**33**).* Compound **32** (60 mg, 0.17 mmol) was treated with acetic acid/water (10 mL of a 2:1 v/v mixture), and the resulting mixture was stirred at 22 °C for 18 h and then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:8:1 v/v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4), compound **33** (43 mg, 81%) as a white powder; mp 191 °C; $[\alpha]^{20}_D$ +7.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.83 (s, 1H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 6.03 (d, *J* = 2.5 Hz, 1H), 4.63 (d, *J* = 3.8 Hz, 1H), 3.97 (m, 1H), 3.92 (s, 3H), 3.84 (dd, *J* = 7.6 and 2.5 Hz, 1H), 3.62 (dd, *J* = 10.3 and 3.8 Hz, 1H), 3.49 (s, 3H), 2.83 (broad, s, 3H) (signal due to a hydroxyl group proton not observed); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 191.3, 151.3, 149.5, 137.4, 132.1, 129.9, 128.6, 128.4, 110.1, 82.9, 72.7, 71.8, 70.2, 57.6, 56.6; IR ν_{max} 3346, 2926, 2839, 2821, 1678, 1586, 1454, 1429, 1383, 1298, 1257, 1145, 1106, 1070, 943, 858, 696 cm^{-1}; MS (ESI, +ve) m/z 643 [(2M + Na)$^+$, 35%], 333 [(M + Na)$^+$, 100]; HRMS (ESI, +ve) (M+Na)$^+$ calcd for $C_{15}H_{18}NaO_7$ 333.0950, found 333.0952.

*(5aS,6S,7S,8S)-6,7-Dihydroxy-4,8-dimethoxy-5a,6,7,8-tetrahydrodibenzo[b,d]-furan-2-carbaldehyde (**7**).* A magnetically stirred solution of phenol **33** (40 mg, 0.13 mmol) in THF (12 mL) was treated with Ph_3P (40 mg, 0.15 mmol), cooled to 0 °C, and treated dropwise with a solution of di-*iso*-propyl azodicarboxylate (25 μL, 0.13 mmol) in THF (1 mL). The reaction mixture thus obtained was stirred at 0 °C for 2 h and then concentrated under reduced pressure, and the ensuing light-yellow oil was subjected to flash chromatography (silica, 3:97 v/v methanol/CH_2Cl_2 elution). Concentration of the relevant fractions (R_f = 0.4 in 0.5:9.5 v/v methanol/CH_2Cl_2) afforded benzofuran **7** (32 mg, 85%) as a clear, light-yellow oil; $[\alpha]^{20}_D$ +92.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.87 (s, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.44 (d, *J* = 1.5 Hz, 1H), 6.19 (t, *J* = 3.6 Hz, 1H), 5.09 (m, 1H), 4.94 (s, 1H), 4.48 (broad s, 1H), 4.09 (m, 1H), 3.95 (s, 3H), 3.81−3.77 (complex m, 2H), 3.49 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 191.1, 157.6, 146.9, 138.0, 133.1, 127.7, 118.2, 117.6, 114.0, 89.1, 83.8, 77.3, 75.6, 57.5, 56.6; IR ν_{max} 3339, 2926, 2892, 2853, 2823, 1686, 1604, 1590, 1437, 1337, 1313, 1185, 1119, 1092, 1069, 997, 920, 721, 694 cm^{-1}; MS (ESI, +ve) m/z 607 [(2M + Na)$^+$, 40%], 315 [(M + Na)$^+$, 100], 293 (23), 195 (30); HRMS (ESI, +ve) (M + Na)$^+$ calcd for $C_{15}H_{16}NaO_6$ 315.0845, found 315.0847.

*(3aS,4S,5R,7aS)-7-Bromo-2,2-dimethyl-5-((tri-iso-propylsilyl)oxy)-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol (**35**).* Tri-*iso*-propylsilyl trifluoromethanesulfonate (620 μL, 2.3 mmol) was added dropwise to a magnetically stirred solution of compound **34**[31] (500 mg, 1.9 mmol) and 2,6-lutidine (880 μL, 7.6 mmol) in CH_2Cl_2 (15 mL) maintained at −78 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 22 °C over 3 h and then treated with NH_4Cl (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (1 × 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate/hexane elution) and gave, after concentration of the appropriate fractions (R_f = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate/CH_2Cl_2/hexane), an ∼6:1 mixture of ether **35** and its regioisomer (700 mg, 88% combined yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (major regioisomer) 6.00 (m, 1H), 4.62 (dd, *J* = 5.2 and 1.5 Hz, 1H), 4.49 (m, 2H), 4.24 (m, 1H), 2.67 (d, *J* = 1.5 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.12−0.99 (complex m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major regioisomer) 130.8, 123.5, 110.0, 75.9, 75.7, 69.3, 68.3, 27.5, 26.2, 17.9(4), 17.9(3), 12.2; IR ν_{max} 3560, 2943, 2893, 2867, 1645, 1463, 1382, 1370, 1340, 1236, 1080, 1055, 882, 863, 682 cm^{-1}; MS (EI, 70 eV) m/z 423 and 421 [(M+ H)$^+$, 10 and 9%], 407 and 405 [(M −

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$CH_3\bullet)^+$, 7 and 6], 321 and 319 (100 and 97); HRMS (EI, 70 eV) (M − $CH_3\bullet)^+$ calcd for $C_{17}H_{30}{}^{79}BrO_4Si$ 405.1097, found 405.1096.

*(((3aS,4S,5R,7aS)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]diox-ol-5-yl)oxy)tri-iso-propylsilane (**36**).* Sodium hydride (172 mg of a 60% dispersion in mineral oil, 4.3 mmol) was added to a magnetically stirred solution of an ∼6:1 mixture of compound **35** and its regioisomer (600 mg, 1.4 mmol) and iodomethane (267 μL, 4.3 mmol) in dry THF (15 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at 22 °C, and then the reaction mixture was treated with ice-water (30 mL) (*CAUTION!* possibility of hydrogen gas evolution). The separated aqueous phase was extracted with ethyl acetate (1 × 15 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate/CH_2Cl_2/hexane), an ∼5:1 mixture of compound **36** and its regioisomer (570 mg, 92% combined yield) as a clear, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major regioisomer) 6.15 (d, *J* = 3.0 Hz, 1H), 4.62 (m, 1H), 4.56 (m, 1H), 4.44 (t, *J* = 5.4 Hz, 1H), 3.70 (m, 1H), 3.54 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.10−0.98 (complex m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major regioisomer) 133.1, 122.2, 109.9, 80.3, 76.9, 75.1, 68.2, 59.7, 27.5, 26.0, 17.9(8), 17.9(6), 12.2; IR ν_{max} 2941, 2887, 2865, 1649, 1460, 1383, 1335, 1241, 1197, 1138, 1121, 1079, 1040, 956, 880, 858, 680 cm^{-1}; MS (ESI, +ve) *m*/*z* 459 and 457 [(M + Na)$^+$, 83 and 81%], 437 and 435 (88 and 86), 205 and 203 (97 and 100); HRMS (ESI, +ve) (M + Na)$^+$ calcd for $C_{19}H_{35}{}^{79}BrNaO_4Si$ 457.1386, found 457.1375.

*(3aS,4R,5R,7aS)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]-dioxol-5-ol (**37**).* A magnetically stirred solution of an ∼5:1 mixture of compound **36** and its regioisomer (600 mg, 1.4 mmol) in THF (10 mL) maintained at 22 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (2 mL of 1.0 M solution in THF, 4.1 mmol). After 2 h, the reaction mixture was concentrated under reduced pressure, and the residue so-formed was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.4 in 4:2.5:5.5 v/v/v ethyl acetate/CH_2Cl_2/hexane) gave compound **37** (338 mg, 88%) as a white powder; mp 61 °C; $[\alpha]^{20}_D$ +15.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 400 MHz) δ 6.15 (d, *J* = 3.0 Hz, 1H), 4.59 (m, 1H), 4.53 (t, *J* = 5.1 Hz, 1H), 4.33 (complex m, 1H), 3.76 (t, *J* = 4.4 Hz, 1H), 3.54 (s, 3H), 2.55 (broad s, 1H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 123.2, 110.3, 78.7, 76.2, 73.9, 66.3, 59.2, 27.6, 26.2; IR ν_{max} 3453, 2987, 2935, 2900, 2831, 1646, 1457, 1381, 1372, 1231, 1109, 1077, 1041, 964, 868 cm^{-1}; MS (EI, 70 eV) (EI, 70 eV) 280 and 278 (M$^{+\bullet}$, both 1%), 265 and 263 (74 and 76), 177 and 175 (13 and 15), 124 (28), 115 (100); HRMS M$^{+\bullet}$ calcd for $C_{10}H_{15}{}^{79}BrO_4$ 278.0154, found 278.0153.

*4-Hydroxy-3-((3aR,6R,7R,7aR)-6-hydroxy-7-methoxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-5-methoxybenzaldehyde (**38**).* A magnetically stirred solution of compound **37** (116 mg, 0.42 mmol), boronate ester **27** (139 mg, 0.50 mmol), $PdCl_2$dppf·CH_2Cl_2 (25 mg, 0.03 mmol), and triethylamine (2 mL) in THF/water (15 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated under reflux for 3 h before being cooled, poured into water (40 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane) gave phenol **38** (80 mg, 55%) as a light-yellow oil; $[\alpha]^{20}_D$ +7.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.39 (d, *J* = 1.5 Hz, 1H), 7.37 (d, *J* = 1.5 Hz, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 5.15 (d, *J* = 5.8 Hz, 1H), 4.64 (t, *J* = 5.5 Hz, 1H), 4.52 (m, 1H), 3.96 (s, 3H), 3.79 (t, *J* = 4.6 Hz, 1H), 3.59 (s, 3H), 2.65 (broad d, *J* = 8.3 Hz, 1H), 1.46 (s, 3H), 1.40 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 149.4, 147.9, 134.8, 132.0, 129.2, 128.3, 125.9, 109.8, 108.4, 79.7, 73.6, 73.3, 65.0, 59.1, 56.3, 27.6, 25.9; IR ν_{max} 3368, 2985, 2936, 1681, 1588, 1456, 1432, 1297, 1149, 1120, 1071, 913, 873 cm^{-1}; MS (EI, 70 eV) *m*/*z* 350 (M$^{+\bullet}$, 4%), 274 (41), 115 (100); HRMS (EI, 70 eV) M$^{+\bullet}$ calcd for $C_{18}H_{22}O_7$ 350.1366, found 350.1370.

*2-((3aS,4R,5R,7aR)-7-(5-Formyl-2,3-dimethoxyphenyl)-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-yl)-N,N-dimethylacetamide (**39**).* A magnetically stirred solution of compound **38** (60 mg, 0.17 mmol) in toluene (10 mL) was treated with *N*,*N*-dimethylacetamide dimethyl acetal (126 μL, 0.87 mmol), and the ensuing mixture was heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.3 in 5:1 v/v ethyl acetate/hexane) then gave an ∼5:1 mixture of amide **39** and its β-epimer (30 mg, 40% combined yield) as a clear, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major epimer) 9.87 (s, 1H), 7.39−7.36 (complex m, 2H), 6.01 (d, *J* = 4.6 Hz, 1H), 5.20 (d, *J* = 6.7 Hz, 1H), 4.41 (t, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.65−3.59 (complex m, 1H), 3.48 (s, 3H), 3.34 (m, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 2.73 (dd, *J* = 15.9 and 5.1 Hz, 1H), 2.27 (dd, *J* = 15.9 and 9.4 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major epimer) 191.2, 171.3, 153.3, 152.1, 134.6, 133.9, 133.1, 132.3, 127.5, 109.6, 109.0, 79.7, 74.4, 73.6, 60.8, 58.1, 56.0, 37.3, 35.5, 33.7, 33.4, 27.9, 25.7; IR ν_{max} 2982, 2932, 2857, 2831, 1691, 1646, 1578, 1458, 1421, 1384, 1240, 1142, 1034, 1002, 913, 863, 733 cm^{-1}; MS (ESI, +ve) *m*/*z* 456 [(M + Na)$^+$, 78%], 434 (100), 376 (21); HRMS (ESI, +ve) (M + Na)$^+$ calcd for $C_{23}H_{31}NNaO_7$ 456.1998, found 456.1996.

*2-((3R,4R,5R,6R)-5′-Formyl-5,6-dihydroxy-2′,3′,4-trimethoxy-3,4,5,6-tetrahydro[1,1′-biphenyl]-3-yl)-N,N-dimethylacetamide (**8**).* An ∼5:1 mixture of compound **39** and its β-epimer (16 mg, 0.04 mmol) was treated with acetic acid/water (10 mL of a 2:1 v/v mixture), and the resulting solution was heated at 50 °C for 22 h and then cooled to 22 °C and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:8:1 v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4 in 1:9 v/v methanol/ethyl acetate), an ∼6:1 mixture of compound **8** and its β-epimer (10 mg, 69% combined yield) as a light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major epimer) 9.87 (s, 1H), 7.39 (complex m, 2H), 5.99 (m, 1H), 4.71 (m, 1H), 4.01 (dd, *J* = 9.2 and 4.0 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.80 (m, 1H), 3.50 (m, 1H), 3.46 (s, 3H), 3.02 (s, 3H), 2.95 (s, 3H), 2.85 (broad s, 1H), 2.74 (dd, *J* = 15.9 and 5.0 Hz, 1H), 2.20 (dd, *J* = 15.9 and 9.0 Hz, 1H) (signal due to a hydroxyl group proton not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major epimer) 191.1, 171.4, 153.2, 151.7, 135.1, 134.9, 133.3, 132.4, 127.5, 109.8, 77.7, 69.0, 68.5, 61.0, 57.9, 56.0, 37.3, 35.6, 34.3, 32.4; IR ν_{max} 3395, 2957, 2935, 2828, 1688, 1627, 1463, 1420, 1387, 1260, 1128, 1105, 1089, 797 cm^{-1}; MS (ESI, +ve) *m*/*z* 787 [(2M + H)$^+$, 30%], 416 [(M + Na)$^+$, 100], 394 (92), 376 (20); HRMS (ESI, +ve) (M + Na)$^+$ calcd for $C_{20}H_{27}NNaO_7$ 416.1685, found 416.1685.

*4-Hydroxy-3-((3aR,6S,7R,7aR)-6-hydroxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-5-methoxybenzaldehyde (**43**).* A magnetically stirred solution of compound **42**[9a] (100 mg, 0.33 mmol), boronate ester **27** (108 mg, 0.39 mmol), $PdCl_2$dppf·CH_2Cl_2 (19 mg, 0.02 mmol), and triethylamine (3 mL) in THF/water (18 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated under reflux for 2 h before being cooled, poured into water (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.3 in 1:3 v/v ethyl acetate/hexane) then gave phenol **43** (60 mg, 49%) as a light-yellow oil; $[\alpha]^{20}_D$ +18.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 7.07 (s, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 5.21 (d, *J* = 6.2 Hz, 1H), 4.90 (d, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.36 (dd, *J* = 8.4 and 6.2 Hz, 1H), 4.27 (broad d, *J* = 8.1 Hz, 1H), 4.08 (d, *J* = 3.3 Hz, 1H),

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3.97 (s, 3H), 3.67 (m, 1H), 3.50 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 149.2, 147.6, 133.6, 131.8, 129.2, 128.5, 125.0, 110.5, 108.1, 98.0, 83.2, 76.5, 74.0, 69.4, 56.4, 55.9, 28.2, 26.0; IR ν_{max} 3370, 2985, 2948, 2936, 1683, 1588, 1488, 1456, 1432, 1372, 1300, 1250, 1217, 1149, 1105, 1058, 1037, 996, 866, 732 cm^{-1}; MS (EI, +ve) m/z 380 ($M^{+\bullet}$, 2%), 362 (12), 260 (59), 259 (54), 231 (100), 218 (48); HRMS (EI, +ve) $M^{+\bullet}$ calcd for $C_{19}H_{24}O_8$ 380.1471, found 380.1478.

*2-((3aS,4R,5R,7aR)-7-(5-Formyl-2,3-dimethoxyphenyl)-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]-dioxol-5-yl)-N,N-dimethylacetamide (**44**).* A magnetically stirred solution of compound **43** (33 mg, 0.09 mmol) in toluene (10 mL) was treated with *N*,*N*-dimethylacetamide dimethyl acetal (64 μL, 0.44 mmol), and the ensuing mixture was heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure, and subjection of the ensuing residue to flash chromatography (silica, 9.5:0.5 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4 in ethyl acetate), an ∼3:1 mixture of amide **44** and its β-epimer (14 mg, 35% combined yield) as a clear, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major epimer) 9.87 (s, 1H), 7.38 (m, 2H), 5.98 (d, J = 4.3 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 4.77 (m, 2H), 4.46 (t, J = 6.5 Hz, 1H), 4.04 (dd, J = 6.9 and 4.5 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.43 (s, 3H), 3.30 (m, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 2.75 (dd, J = 15.8 and 5.1 Hz, 1H), 2.33 (dd, J = 15.8 and 9.5 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (mixture of epimers) (100 MHz, $CDCl_3$) δ 191.3, 171.2, 153.3, 152.0, 134.6, 134.0, 133.0, 132.3, 129.3, 127.7, 113.8, 109.6, 109.2, 100.0, 96.5, 76.2, 75.0, 74.1, 73.8, 60.8, 56.0, 55.7, 37.2, 35.5, 34.2, 33.8, 28.0, 27.9, 26.0; IR ν_{max} 2982, 2933, 2843, 1692, 1647, 1579, 1455, 1384, 1243, 1145, 1070, 1037, 918, 863 cm^{-1}; MS (ESI, +ve) m/z 486 [$(M + Na)^+$, 100%], 464 (3), 60 (10); HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{24}H_{33}NNaO_8$ 486.2104, found 486.2105.

*2-((3R,4R,5R,6R)-5′-Formyl-5,6-dihydroxy-2′,3′-dimethoxy-4-(methoxymethoxy)-3,4,5,6-tetrahydro[1,1′-biphenyl]-3-yl)-N,N-dimethylacetamide (**9**).* Compound **44** (8 mg, 0.02 mmol) was treated with acetic acid/water (10 mL of a 2:1 v/v mixture), and the resulting solution was heated at 50 °C for 22 h and then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:8:1 v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4 in 1:9 v/v methanol/ethyl acetate), an ∼6.5:1 mixture of compound **9** and its β-epimer (5 mg, 69%) as a light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major epimer) 9.87 (s, 1H), 7.38 (m, 2H), 5.97 (d, J = 4.4 Hz, 1H), 4.76−4.71 (complex m, 3H), 4.14 (dd, J = 9.1 and 5.7 Hz, 1H), 4.01 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.45 (s, 3H), 3.34 (broad s, 1H), 3.02 (s, 3H), 2.94 (s, 3H), 2.84 (dd, J = 15.9 and 5.2 Hz, 1H), 2.25 (dd, J = 15.9 and 8.9 Hz, 1H) (signal due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major epimer) 191.2, 171.4, 153.2, 151.7, 135.2, 135.0, 133.3, 132.5, 127.4, 109.8, 97.5, 76.9, 69.2, 68.9, 61.0, 56.0(1), 55.9(6), 37.3, 35.8, 35.6, 33.2; IR ν_{max} 3384, 2919, 2848, 1688, 1630, 1579, 1463, 1419, 1387, 1329, 1292, 1245, 1147, 1130, 1037, 917, 862 cm^{-1}; MS (ESI, +ve) m/z 446 [$(M + Na)^+$, 68%], 424 (100); HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{21}H_{29}NNaO_8$ 446.1791, found 446.1780.

Crystallographic Studies. *Crystallographic Data.* Compound *ent*-**2**. $C_{17}H_{19}NO_5$, M = 317.34, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.58612(5) Å, b = 9.28140(8) Å, c = 23.3001(2) Å; V = 1424.30(2) Å^3, D_x = 1.480 g cm^{-3}, 2794 unique data ($2\theta_{max}$ = 144.6°), R = 0.027 [for 2725 reflections with $I > 2.0\sigma(I)$]; Rw = 0.072 (all data), S = 1.01.

Compound *ent*-**15**. $C_{23}H_{31}NO_7$, M = 433.50, T = 150 K, monoclinic, space group $P2_1$, Z = 2, a = 10.14845(9) Å, b = 10.61199(7) Å, c = 10.80864(10) Å; β = 106.8796(9)°; V = 1113.89(2) Å^3, D_x = 1.292 g cm^{-3}, 3907 unique data ($2\theta_{max}$ = 144.8°), R = 0.026 [for 3843 reflections with $I > 2.0\sigma(I)$]; Rw = 0.067 (all data), S = 1.03.

Compound **27**. $C_{14}H_{19}BO_5$, M = 278.11, T = 150 K, orthorhombic, space group *Pbam*, Z = 8, a = 23.0535(6) Å, b = 18.2756(6) Å, c = 6.8183(2) Å; V = 2872.66(15) Å^3, D_x = 1.286 g cm^{-3}, 3098 unique data ($2\theta_{max}$ = 145.2°), R = 0.084 [for 2982 reflections with $I > 2.0\sigma(I)$]; Rw = 0.191 (all data), S = 1.06.

Compound **32**. $C_{18}H_{22}O_7$, M = 359.38, T = 150 K, monoclinic, space group $P2_1$, Z = 4, a = 7.3153(1) Å, b = 31.4358(3) Å, c = 7.8245(1) Å; β = 94.8743(8)°; V = 1792.83(4) Å^3, D_x = 1.331 g cm^{-3}, 7018 unique data ($2\theta_{max}$ = 145°), R = 0.030 [for 6919 reflections with $I > 2.0\sigma(I)$]; Rw = 0.080 (all data), S = 0.99.

Structure Determination. Diffraction images for compounds *ent*-**2**, *ent*-**15**, **27**, and **32** were all measured on a diffractometer (Mo Kα, mirror monochromator, λ = 0.71073 Å or, for **32**, Cu Kα mirror monochromator, λ = 1.54184 Å) fitted with an area detector, and the data were extracted using the DENZO/Scalepack package.[43] The structure solutions for all four compounds were solved by direct methods (SIR92)[44] and then refined using the CRYSTALS program package.[45] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1517512, 1517513, 1517514 and 1517515). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

AChE Inhibition Testing. The galanthamine derivatives/analogues described above were tested for inhibition against AChE as described by Sangnoi et al.[46] Thus, the compounds were dissolved in DMSO and made up to concentrations ranging from 5 mM to 3.05 μM by serial dilution with DMSO. Then, 2.5 μL of a solution of each compound was added to a solution of 5,5′-dithiobis(2-nitrobenzoic acid) (125 μL of a 1.5 mM aqueous solution), tris(hydroxymethyl)-aminomethane buffer (72.5 μL of a 15 mM solution at pH 8.0), and acetylthiocholine iodide (25 μL of a 150 μM aqueous solution) in water. Enzyme activity was followed after the addition of AChE (25 μL of 0.03 μM solution of *Electrophorus electricus*, Type V−S, EC 3.1.1.7) by measuring the absorption at 412 nm using a microplate spectrophotometer. Assays were repeated in triplicate, and the hydrolysis rate was calculated during the data from the absorptions observed over the first 2 min. Standard commercially available graphic software was used to calculate the tabulated IC_{50} values.

Molecular Docking Studies. The three-dimensional coordinates of each compound were generated with the PRODRG server (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg).[47] Galanthamine and the above-mentioned derivatives/analogues were docked into the structure of human acetylcholine esterase (4EY6) using Autodock Vina v1.1.2 after removal of galanthamine from the active site gorge.[48]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01062.

Data derived from the single-crystal X-ray analyses of compounds *ent*-**2**, *ent*-**15**, **27**, and **32** and ^{1}H and ^{13}C NMR spectra of compounds **2**-**9**, *ent*-**11**, **13**-**17**, **21**, **23**, **24**, **25**, **27**, **29**−**33**, **35**−**39**, **43**, and **44** (PDF)

CIFs of compounds ent-2, ent-15, 27, and 32 (CCDC Nos. 1517512, 1517513, 1517514, and 1517515, respectively)

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION FOR:

The Synthesis of Certain Derivatives and Analogues of (–)- and (+)-Galanthamine and an Assessment of their Capacities to Inhibit Acetylcholine Esterase

Joshua N. Buckler, Ehab S. Taher, Nicolas J. Fraser, Anthony C. Willis, Paul D. Carr,

Colin J. Jackson and Martin G. Banwell*

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

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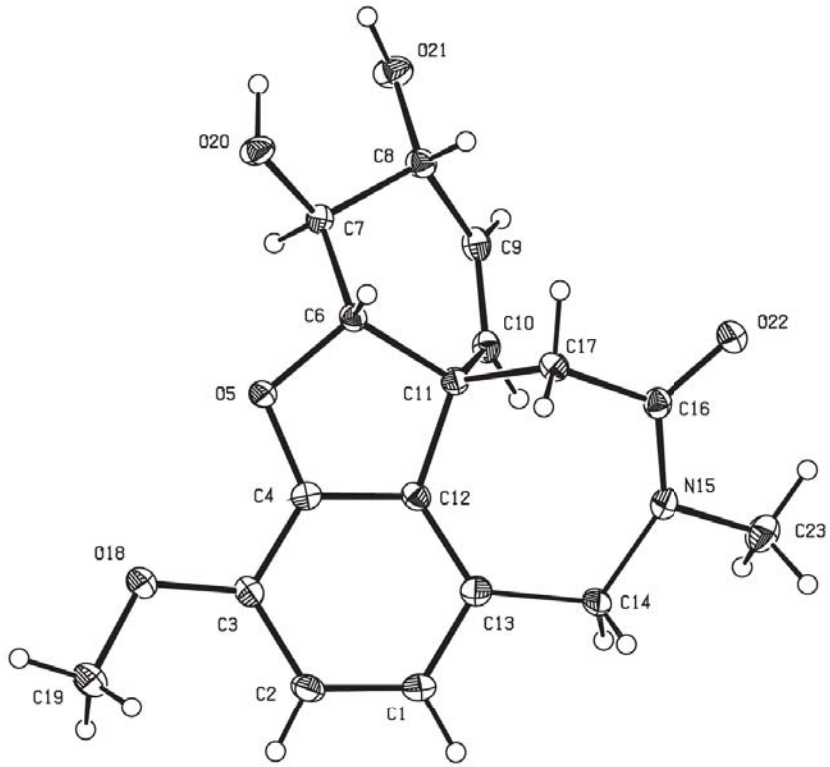
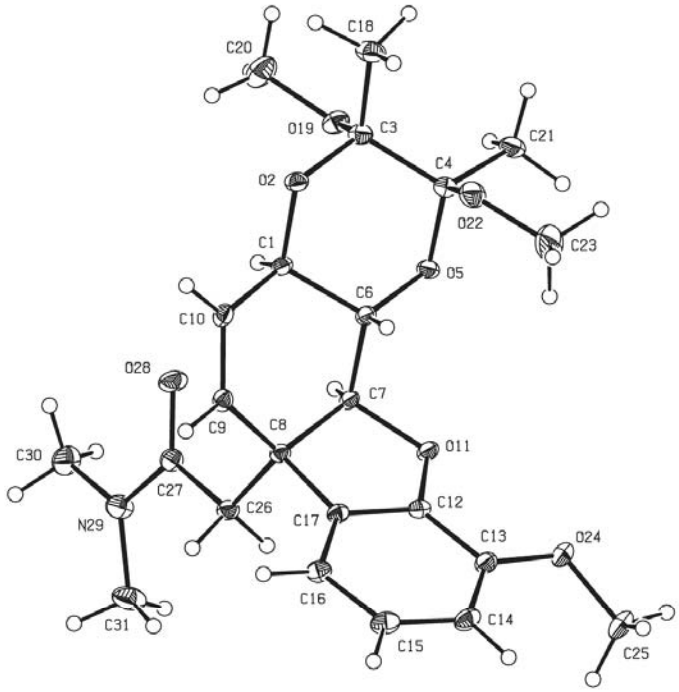


Figure S1: Structure of compound *ent*-**2** (CCDC 1517512) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



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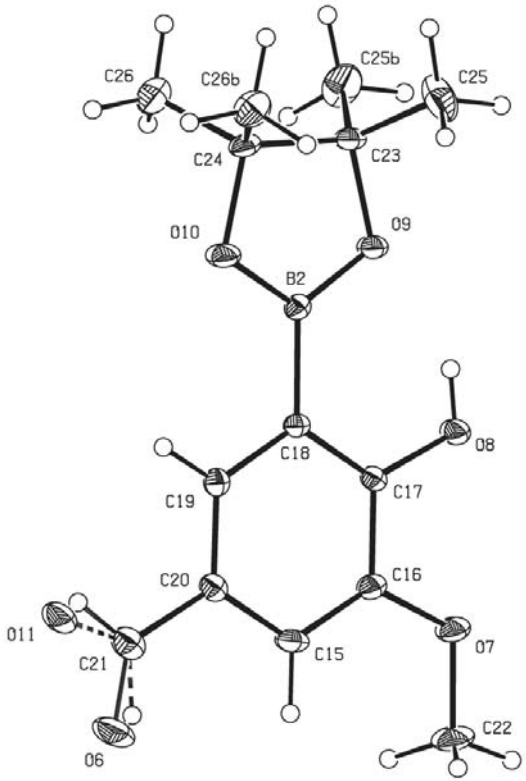


Figure S3: Structure of compound **27** (CCDC 1517514) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

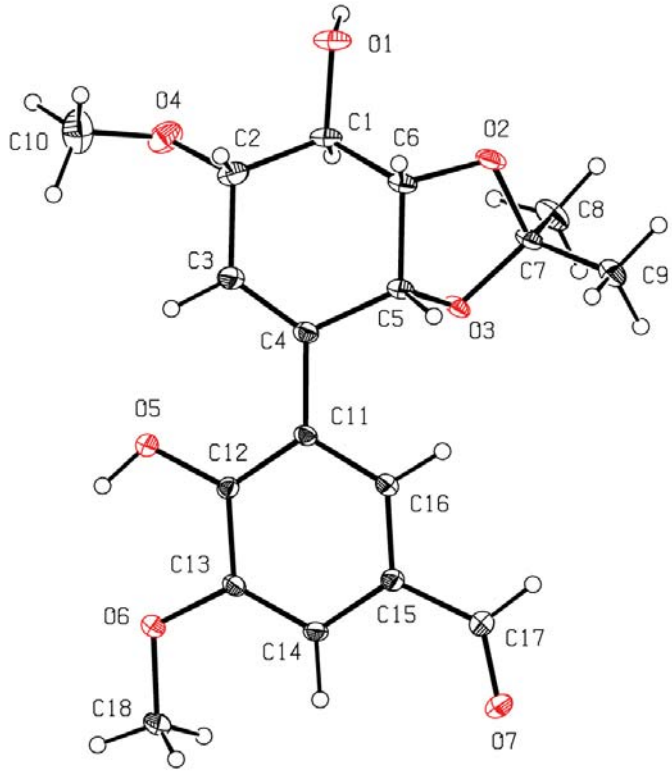
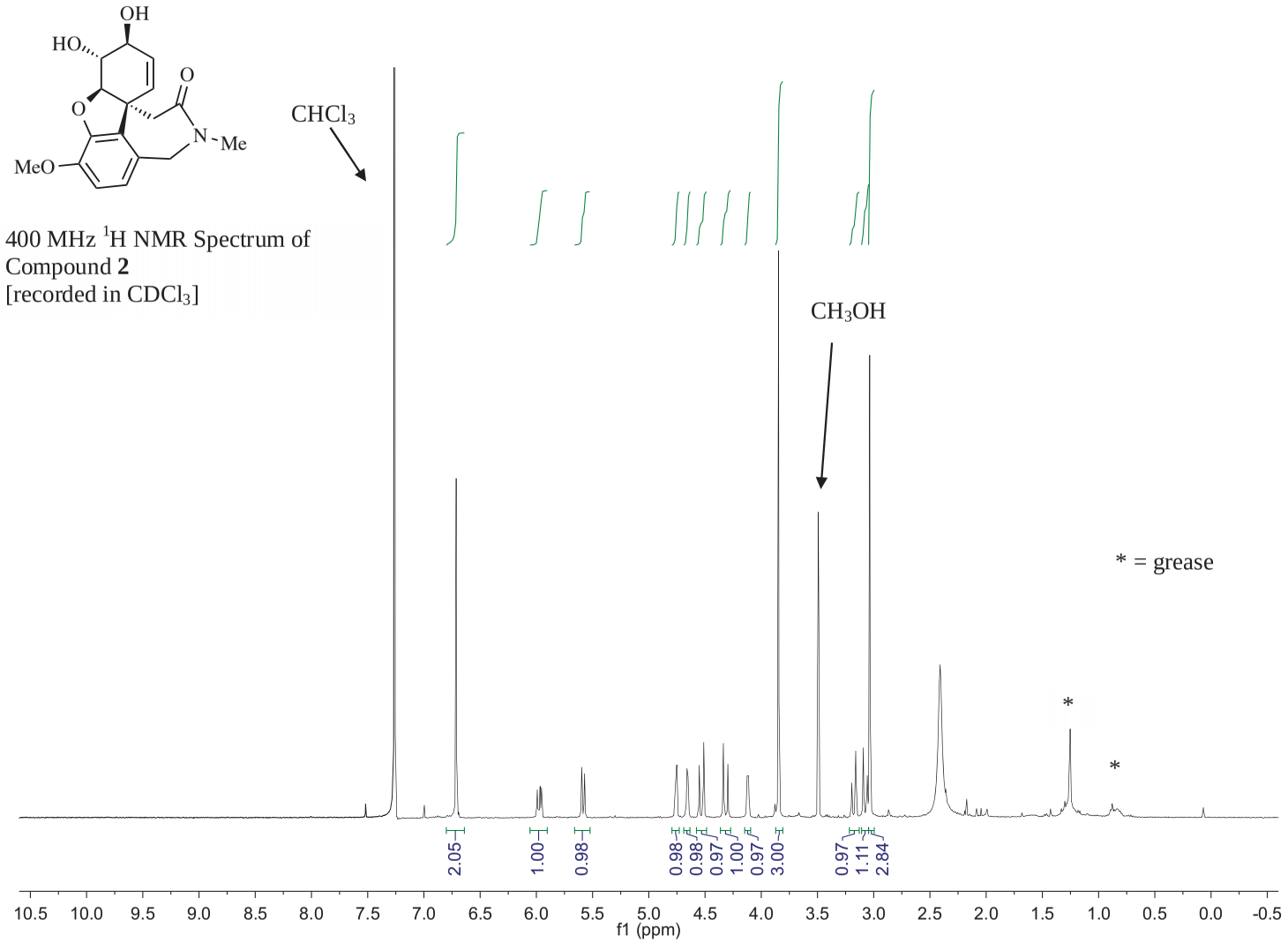
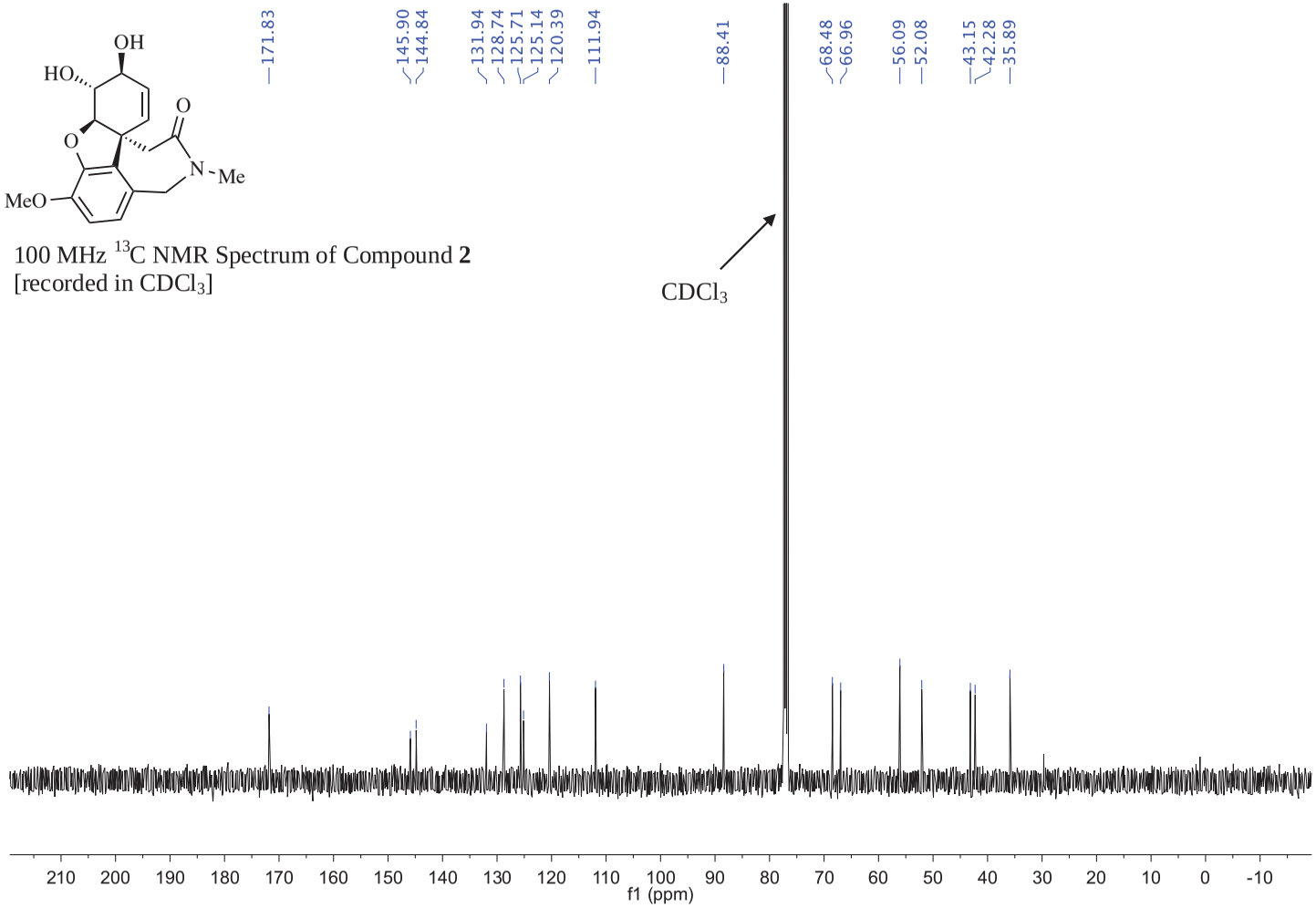


Figure S4: Structure of compound **32** (CCDC 1517515) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



400 MHz ^{1}H NMR Spectrum of Compound **2** [recorded in $CDCl_3$]



100 MHz ^{13}C NMR Spectrum of Compound **2**
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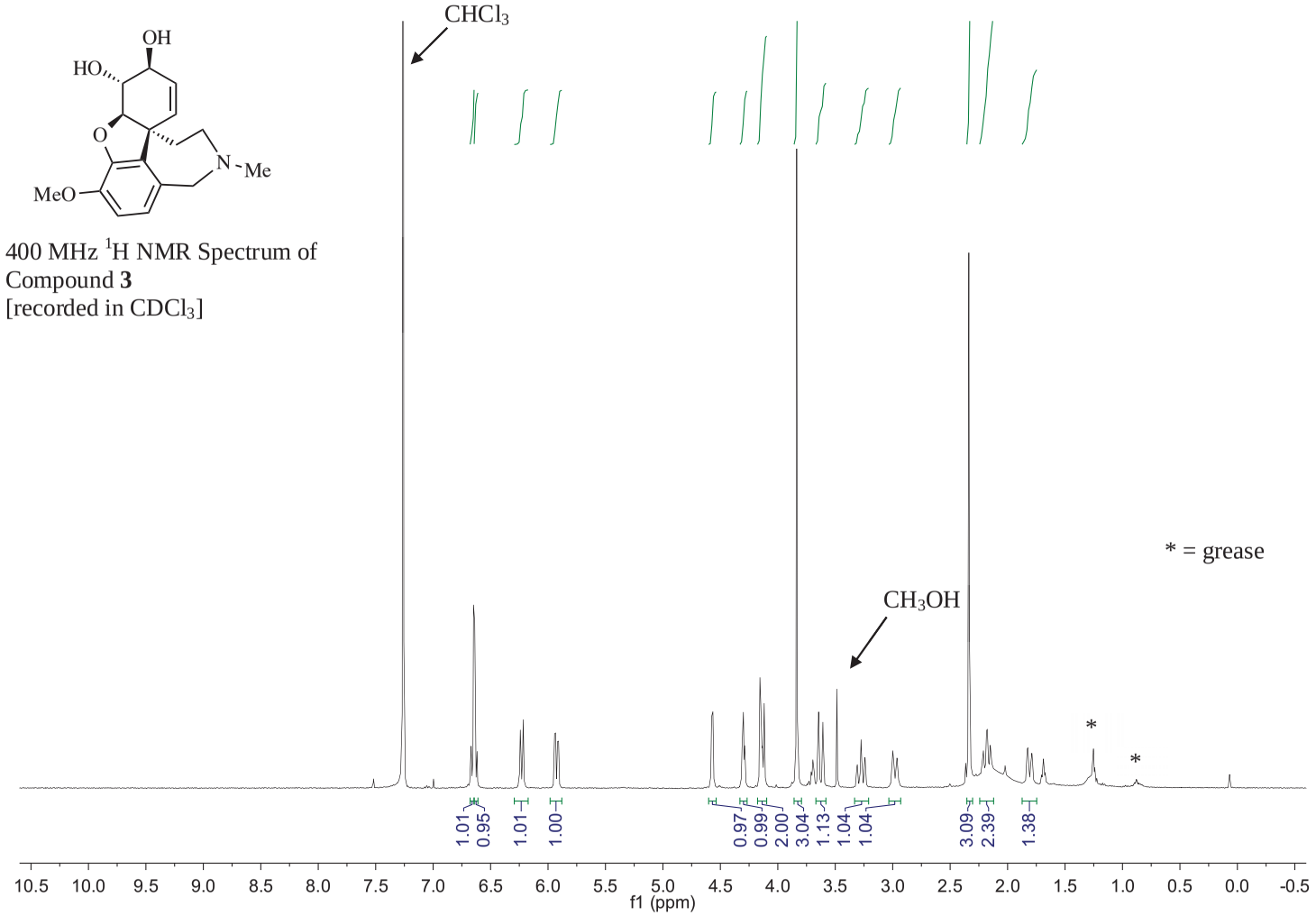

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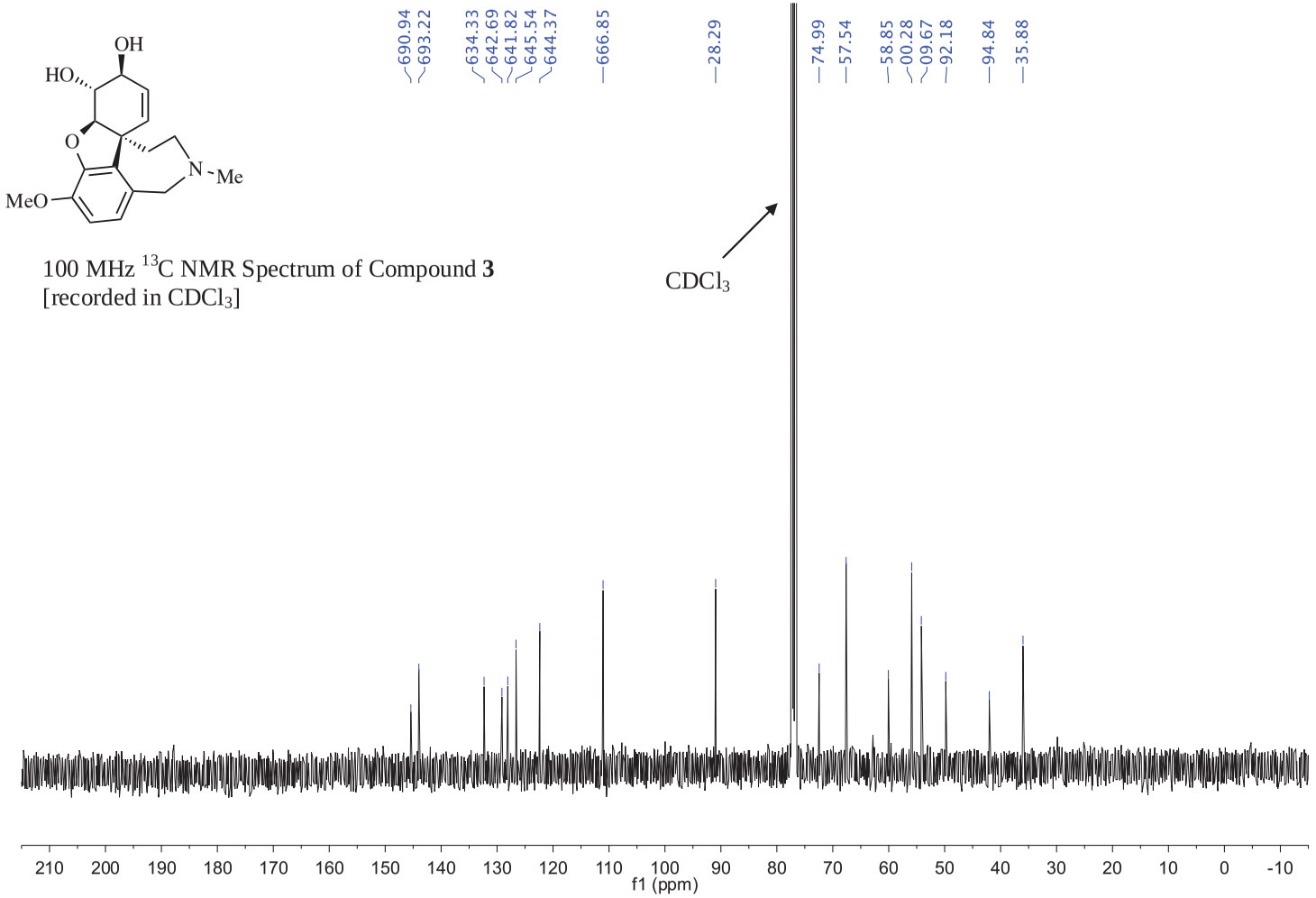

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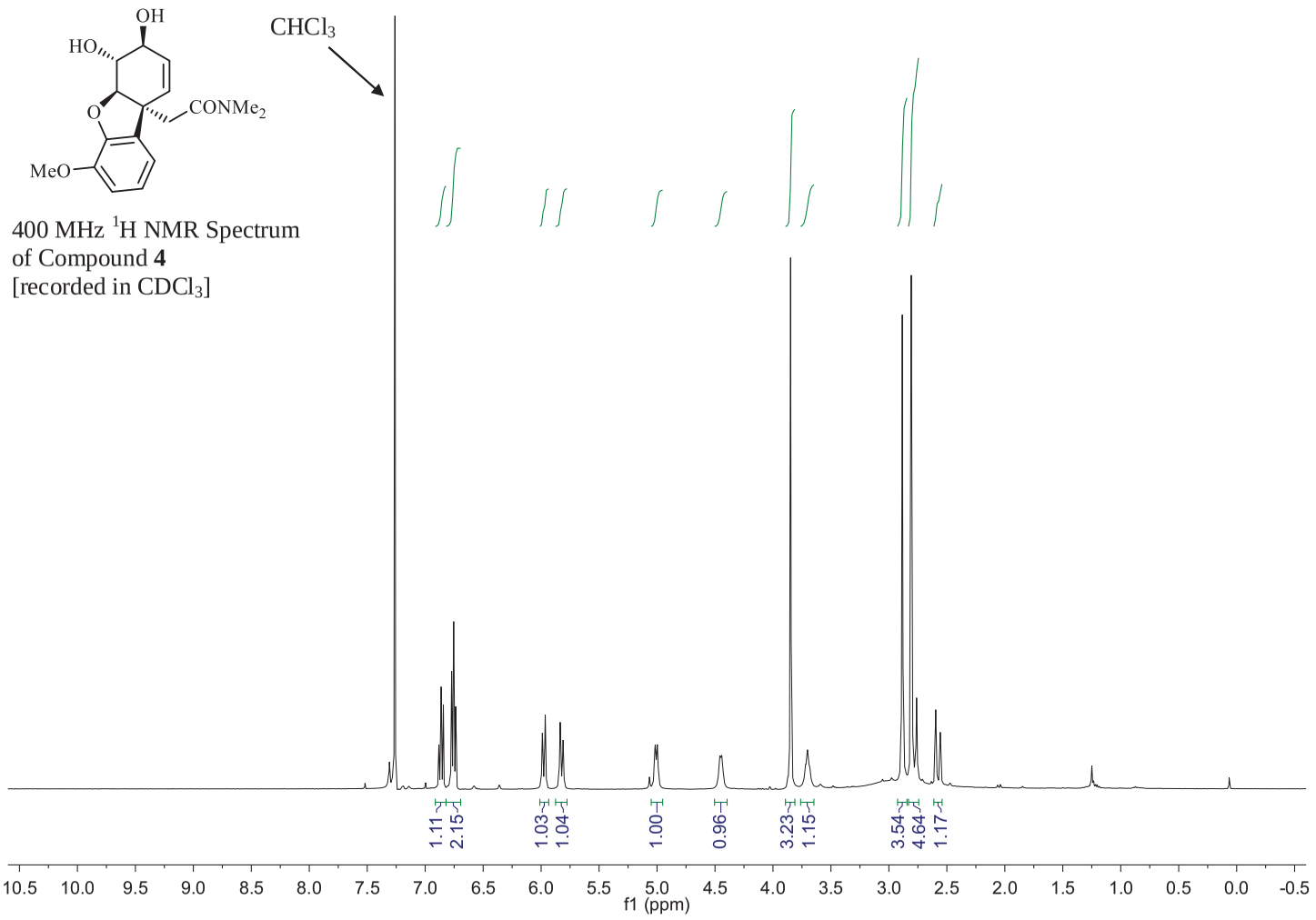

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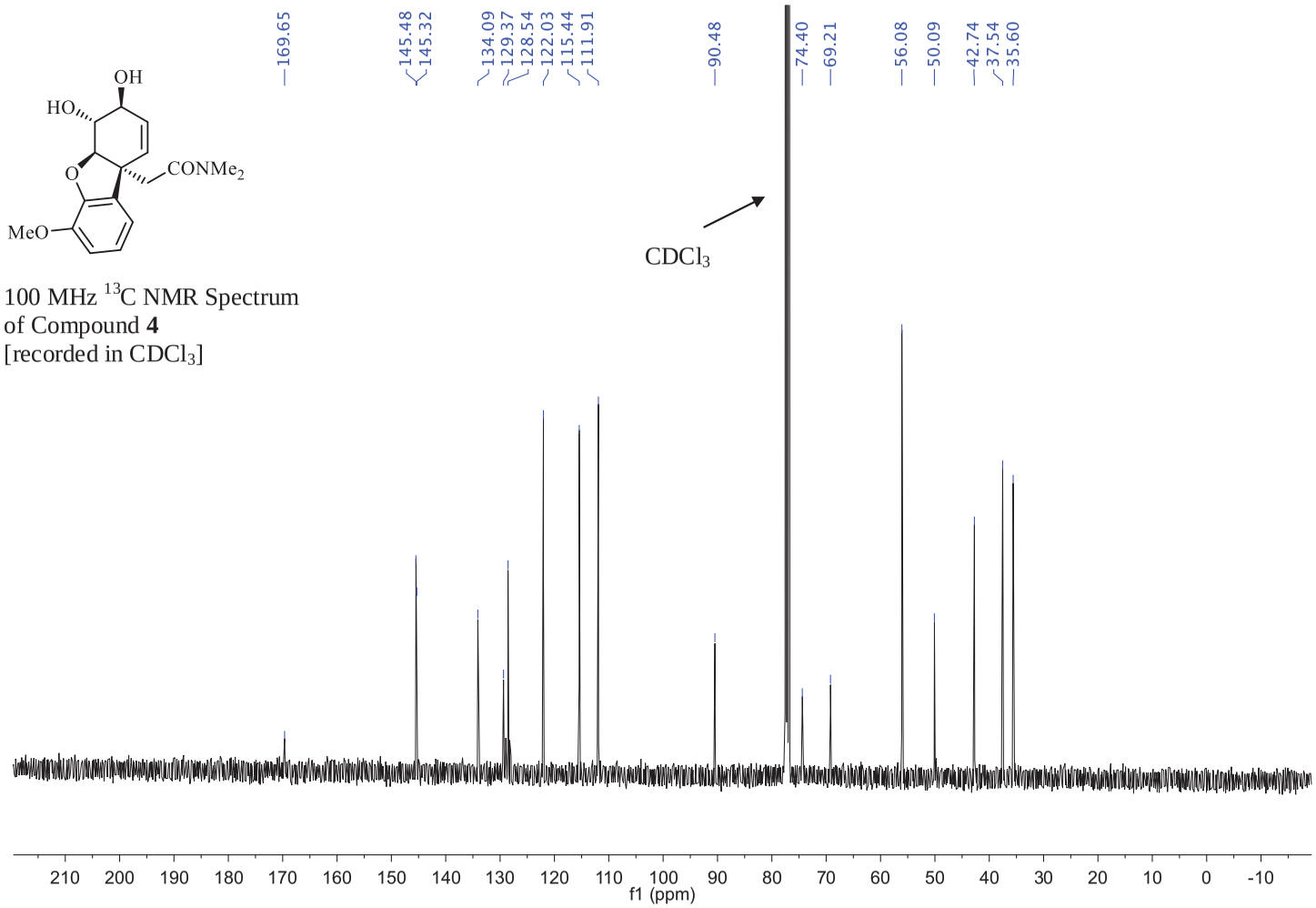

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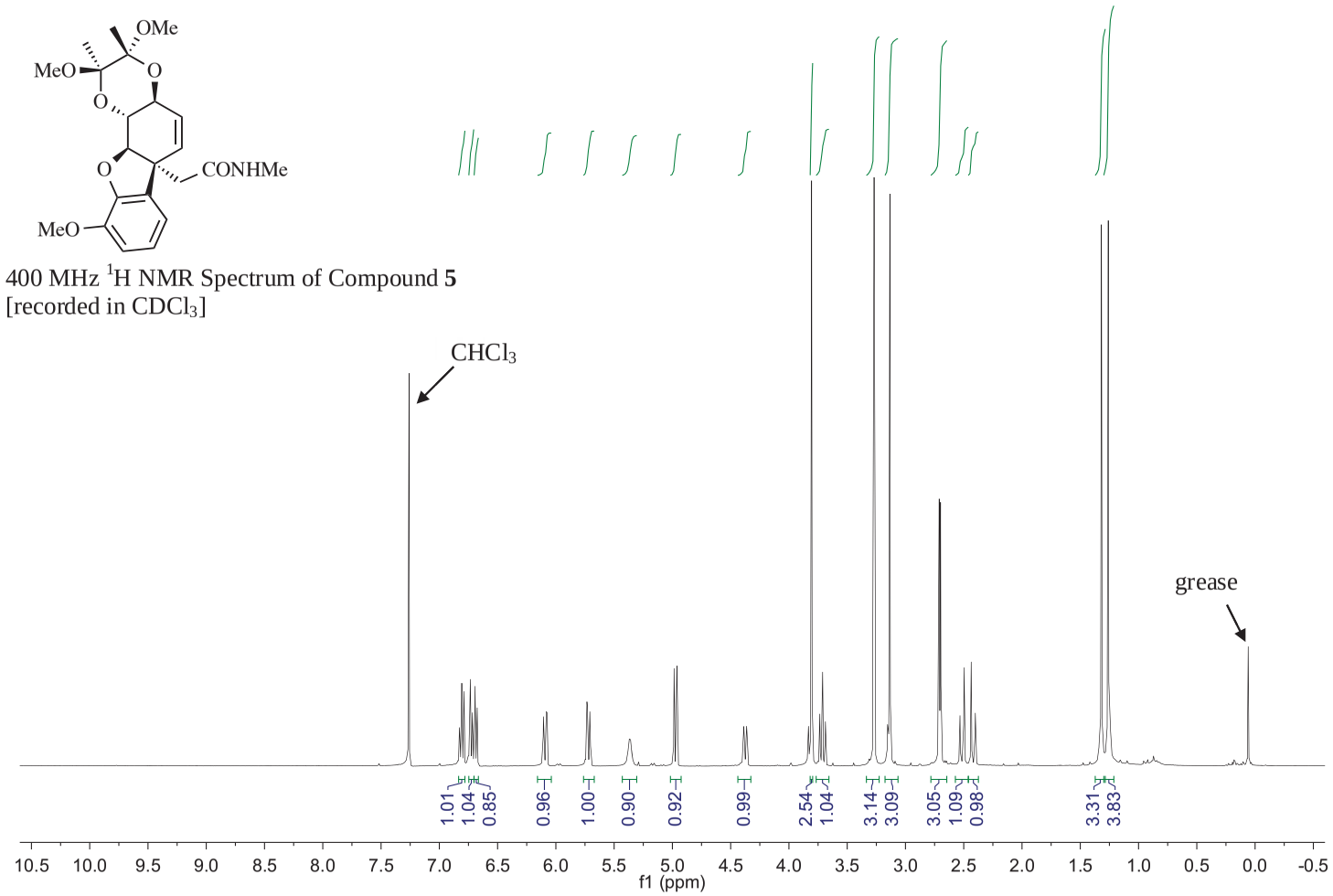

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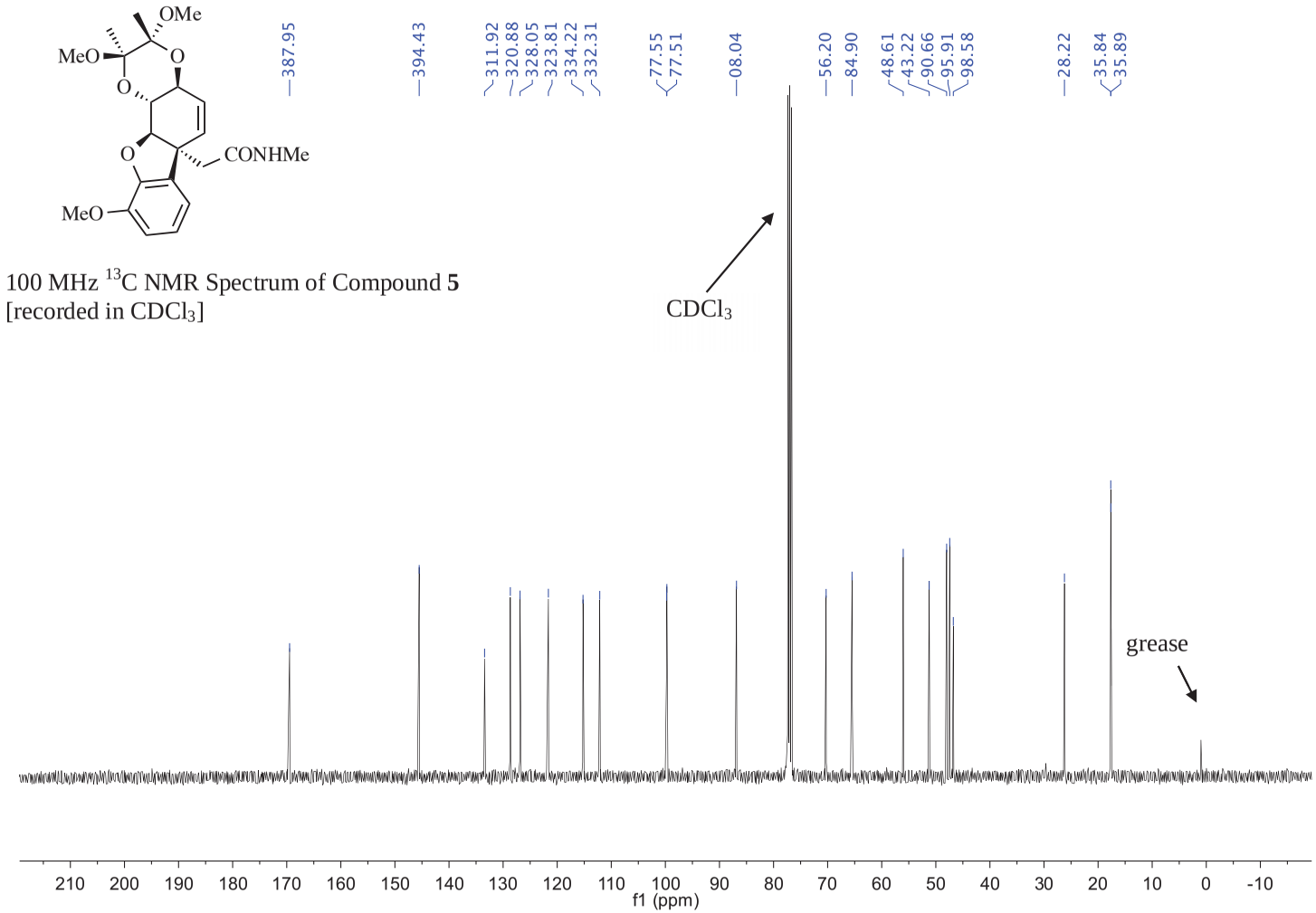

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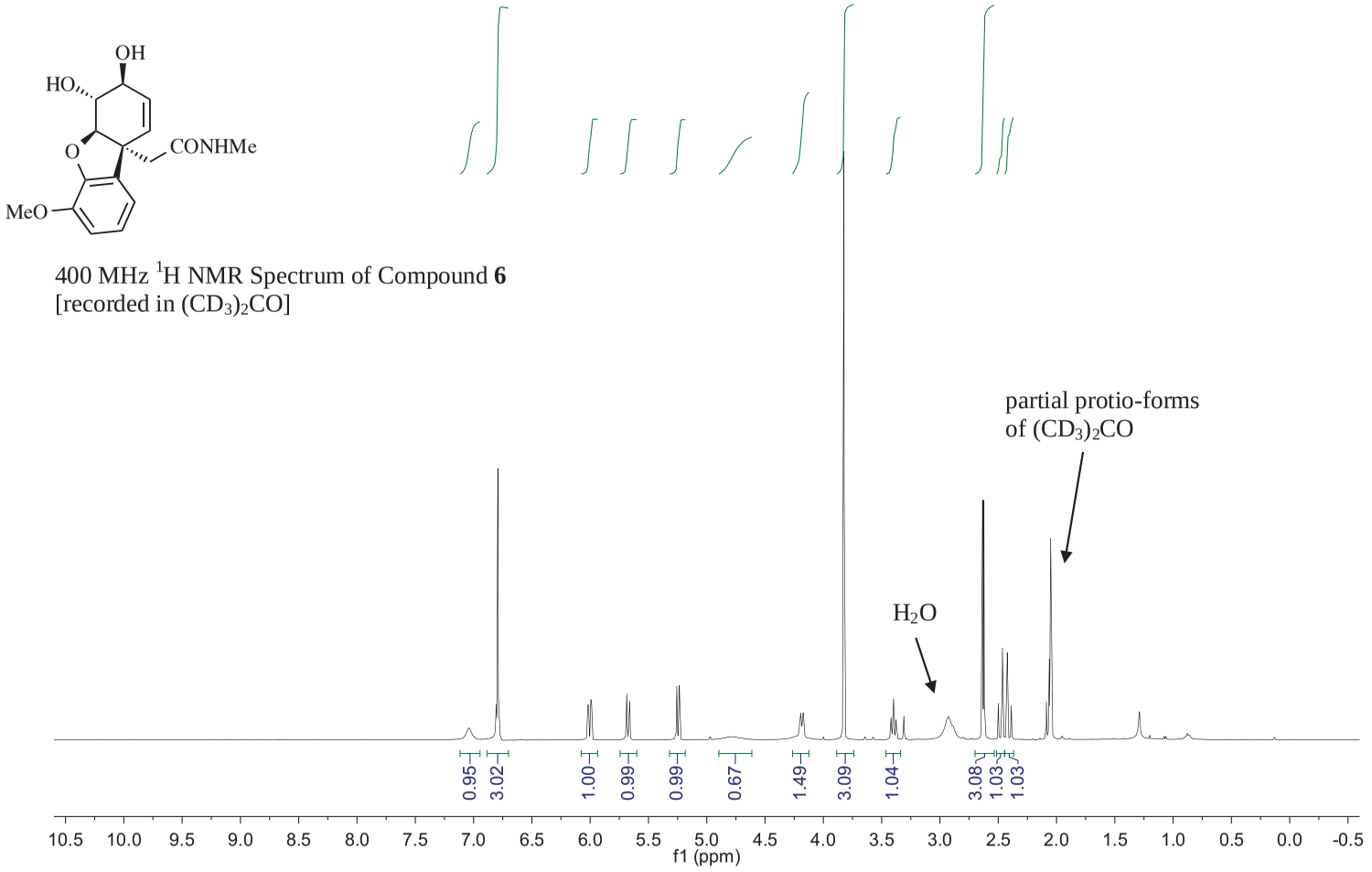

400 MHz ^{1}H NMR Spectrum of Compound **6**
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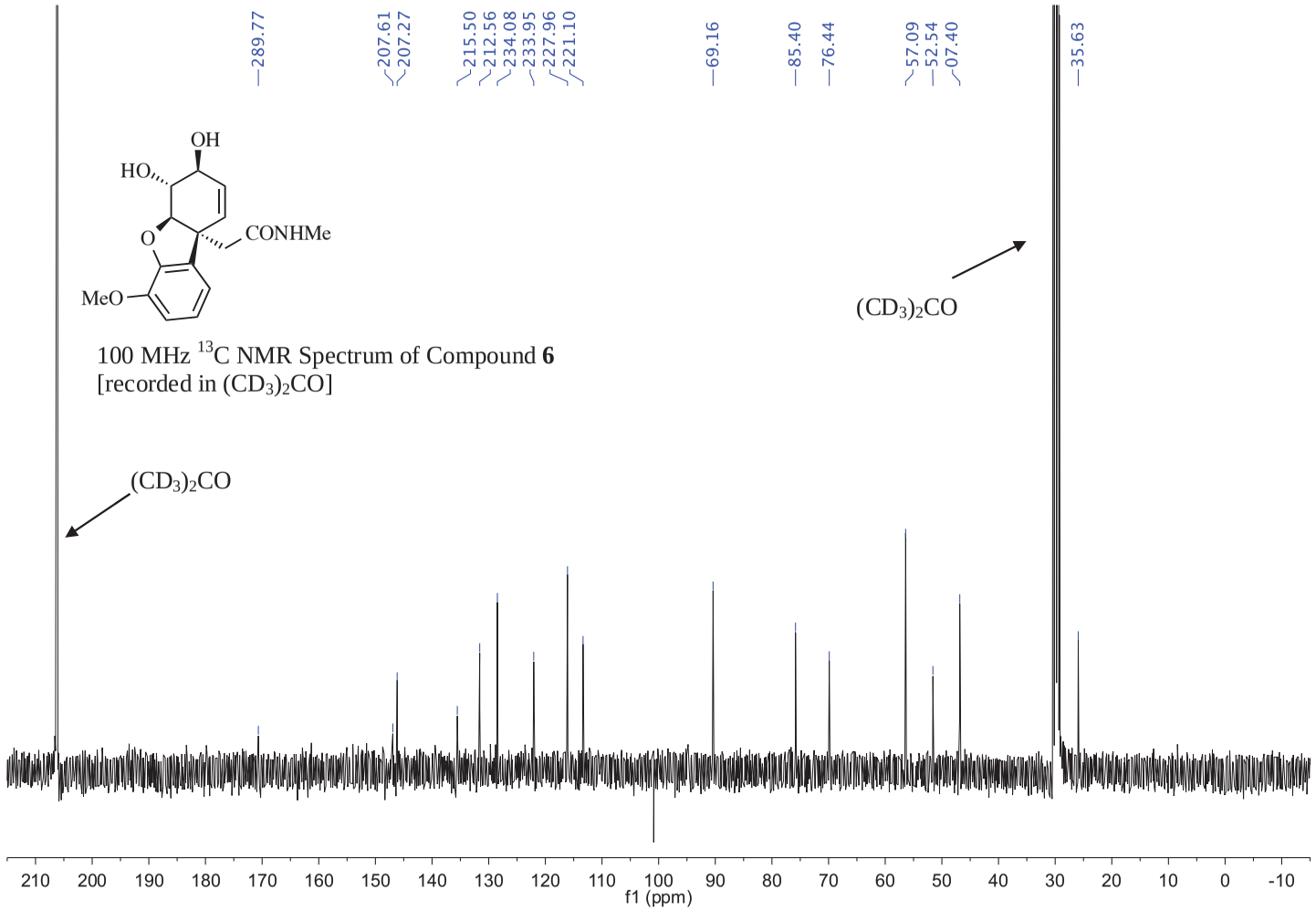

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400 MHz ^{1}H NMR Spectrum of Compound **7**
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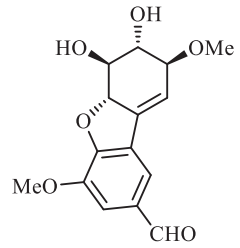

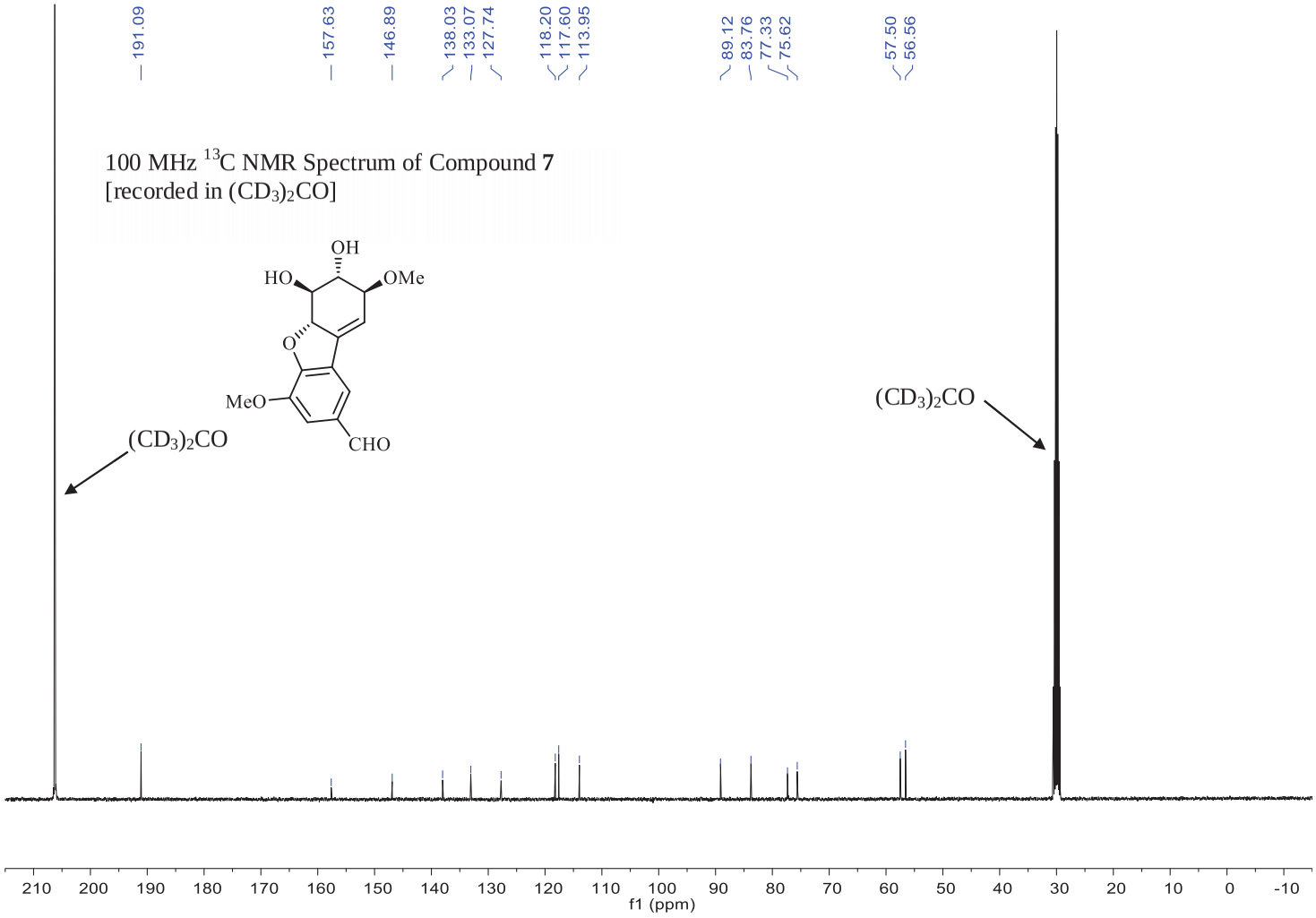
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57.50
56.56
100 MHz ^{13}C NMR Spectrum of Compound **7**
[recorded in $(CD_3)_2CO$]
OH
HO
OMe
O
MeO
CHO
$(CD_3)_2CO$
$(CD_3)_2CO$
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f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **8**
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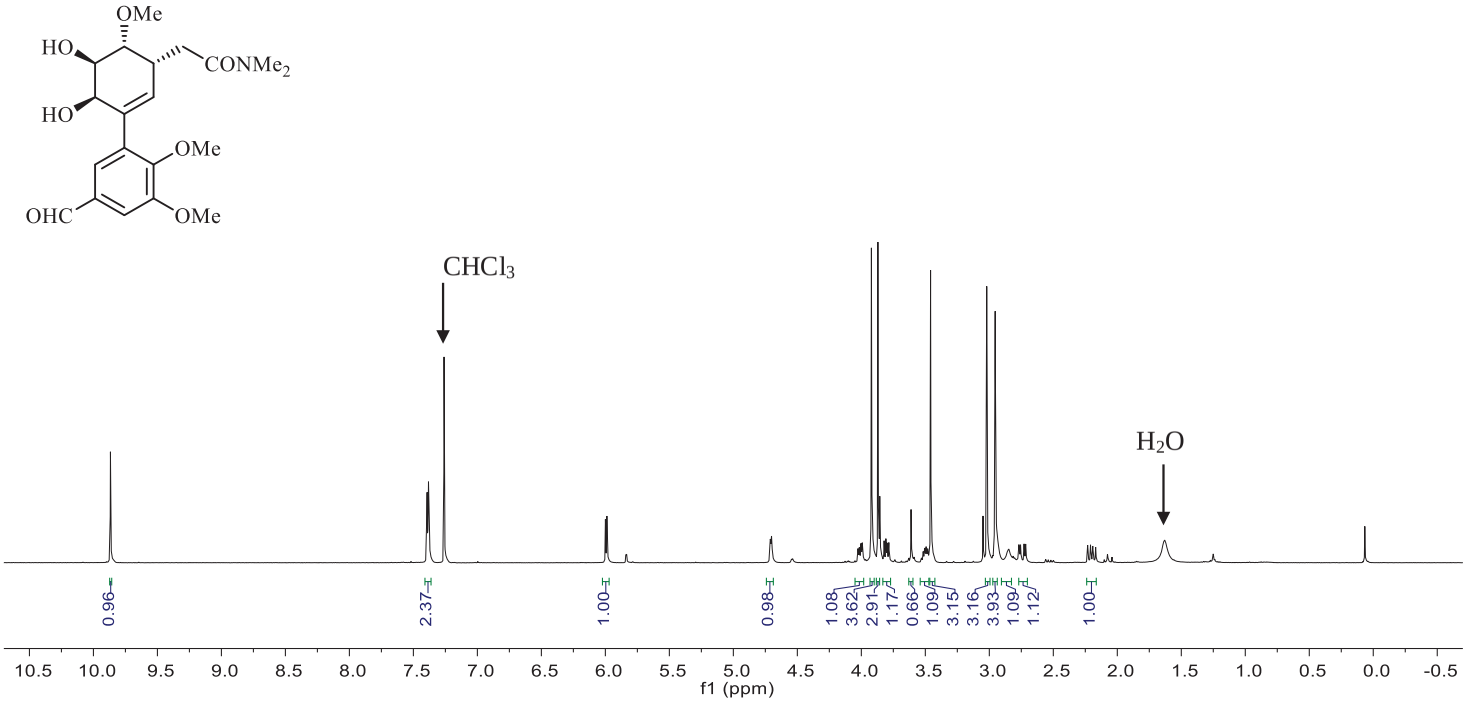

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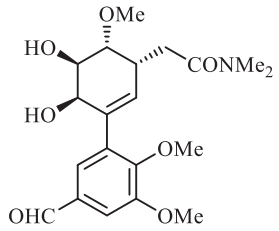

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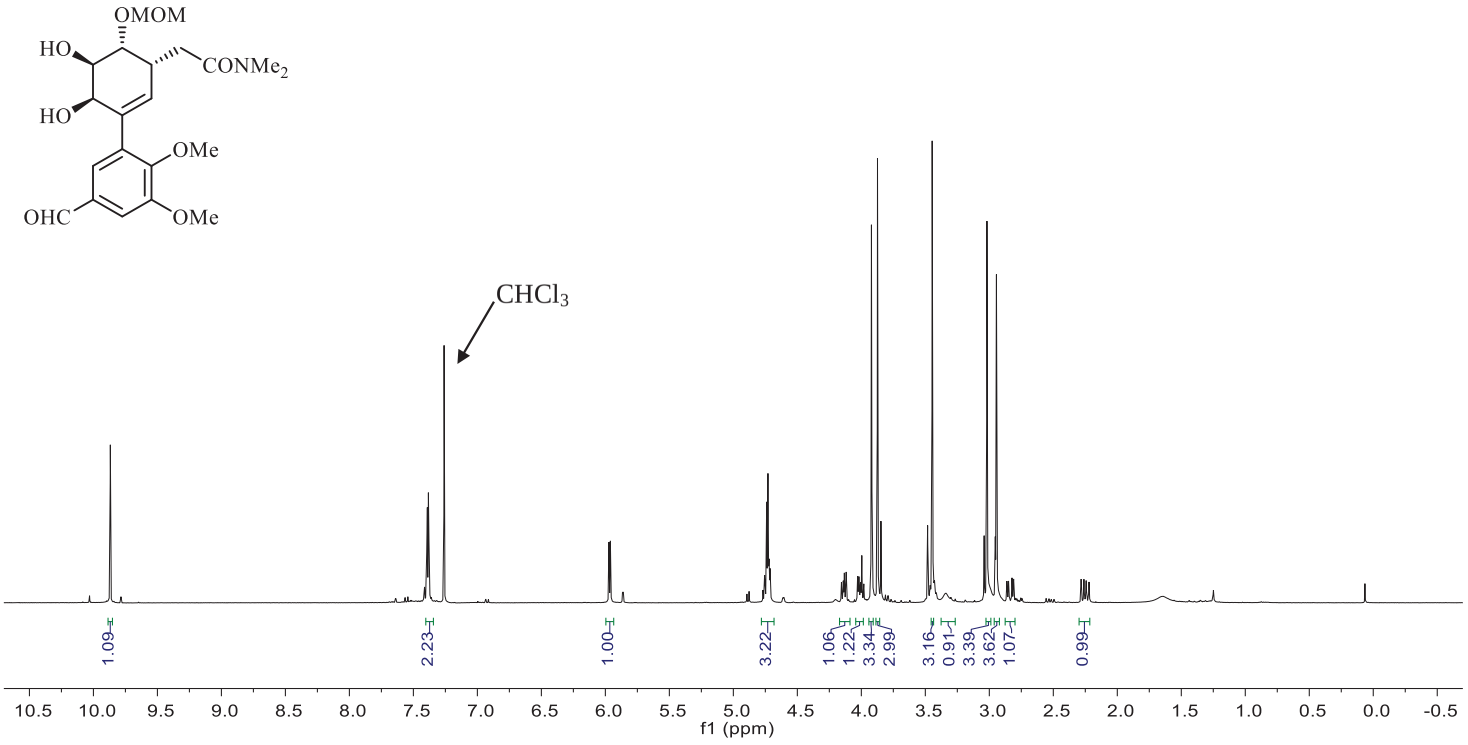

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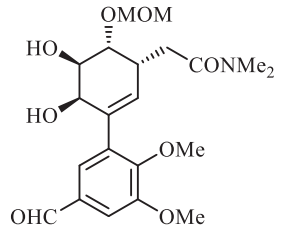
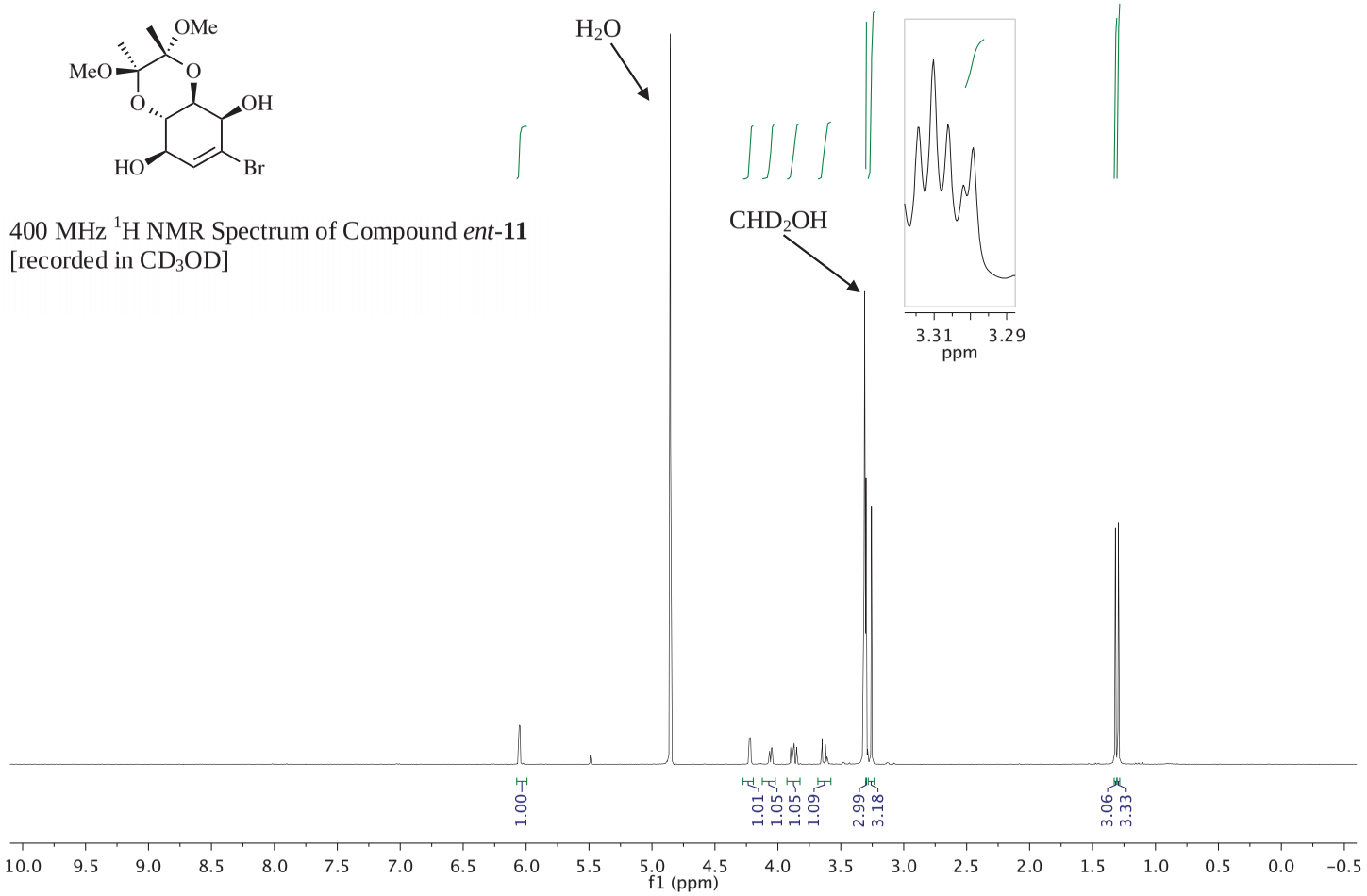
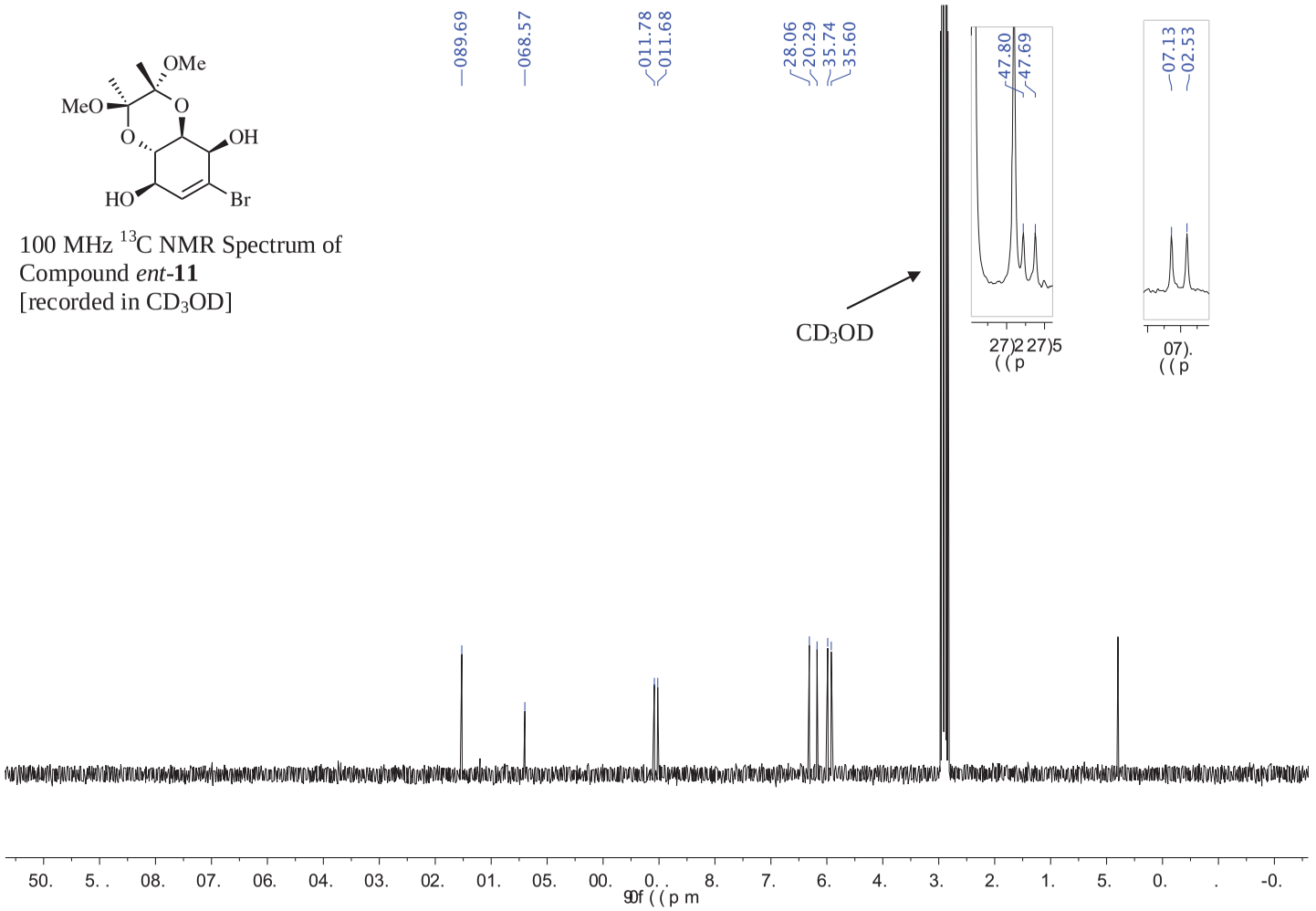
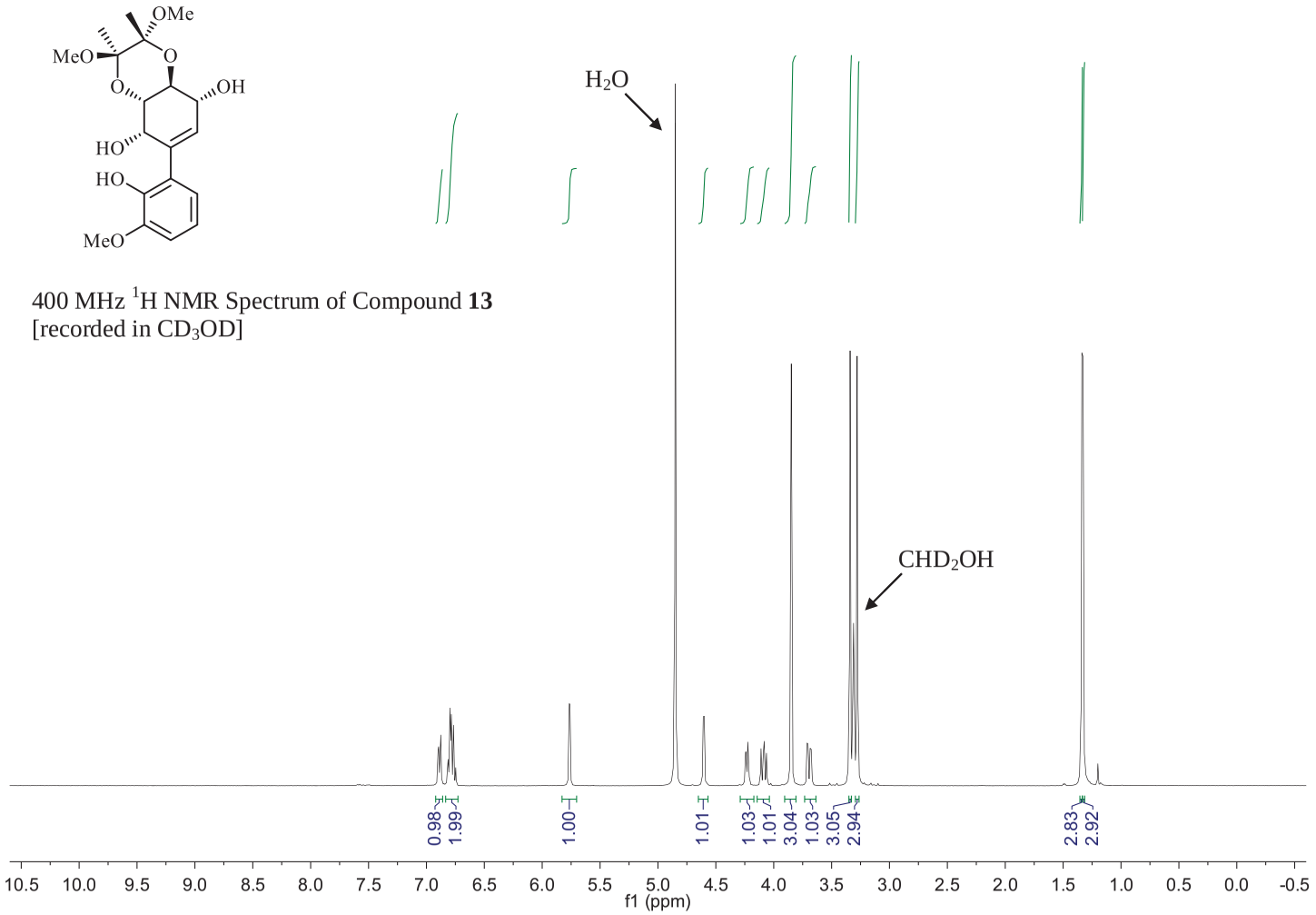




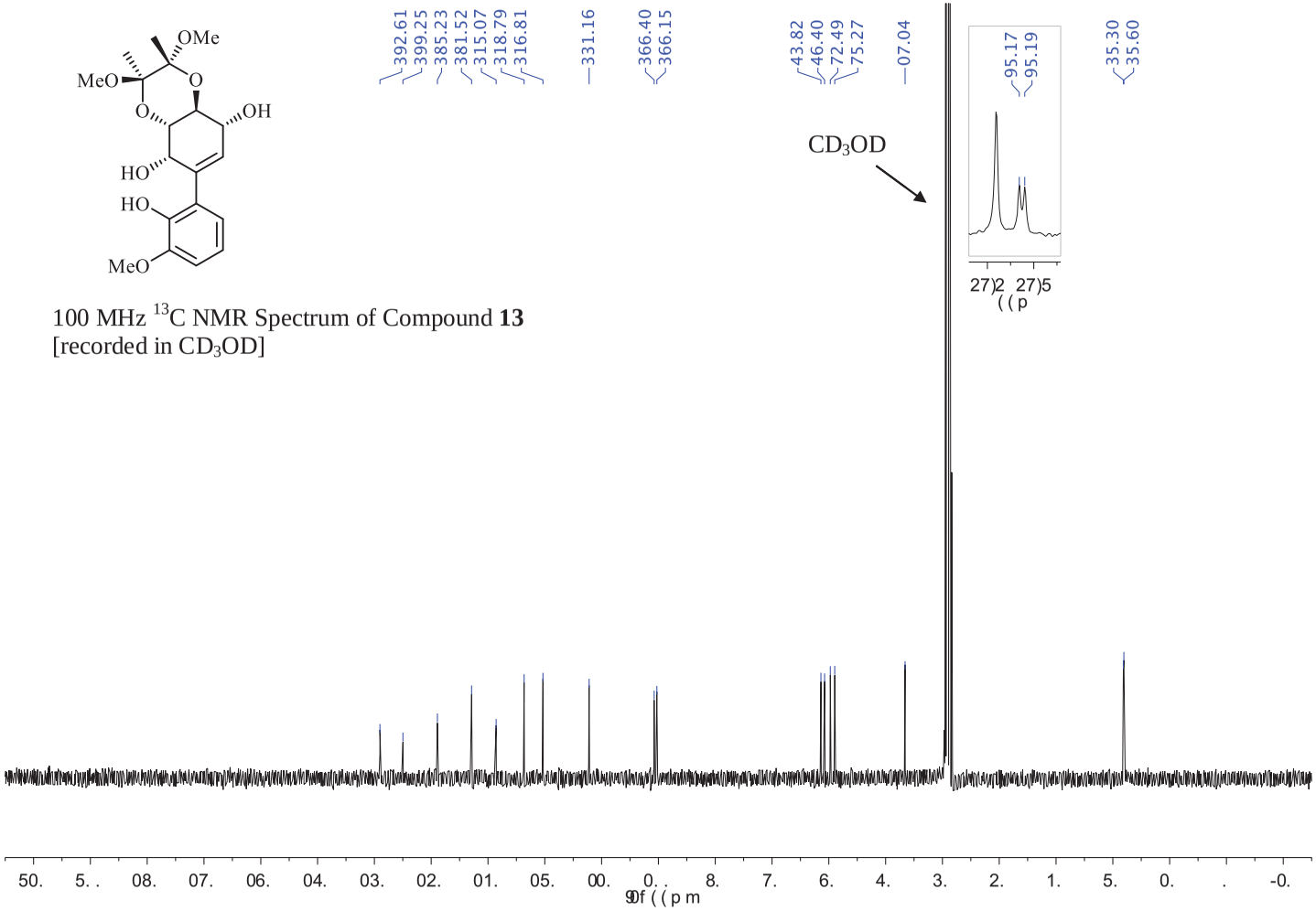
400 MHz ^{1}H NMR Spectrum of Compound *ent*-**11**
[recorded in CD_3OD]



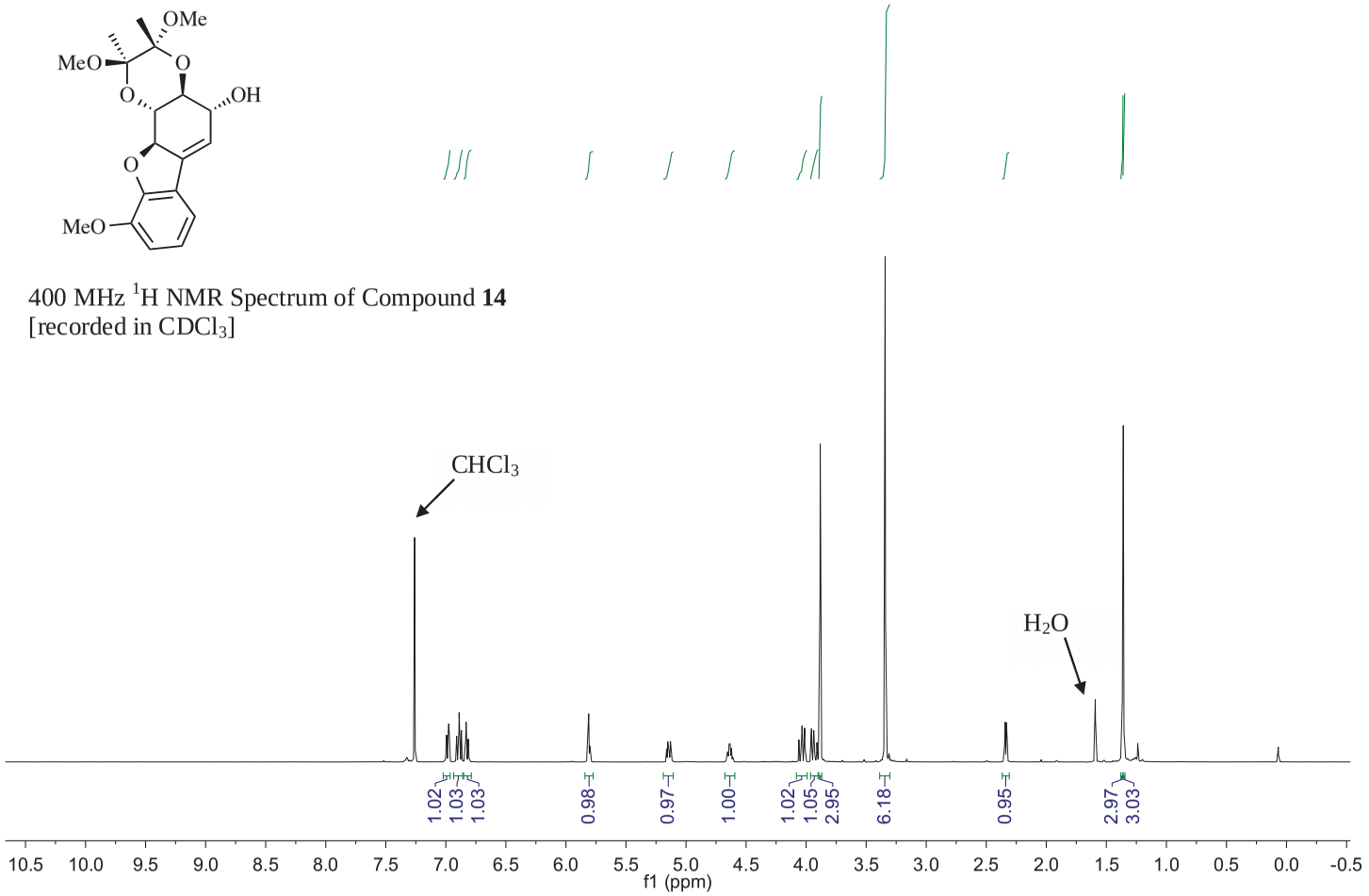
100 MHz ^{13}C NMR Spectrum of Compound *ent*-**11** [recorded in CD_3OD]



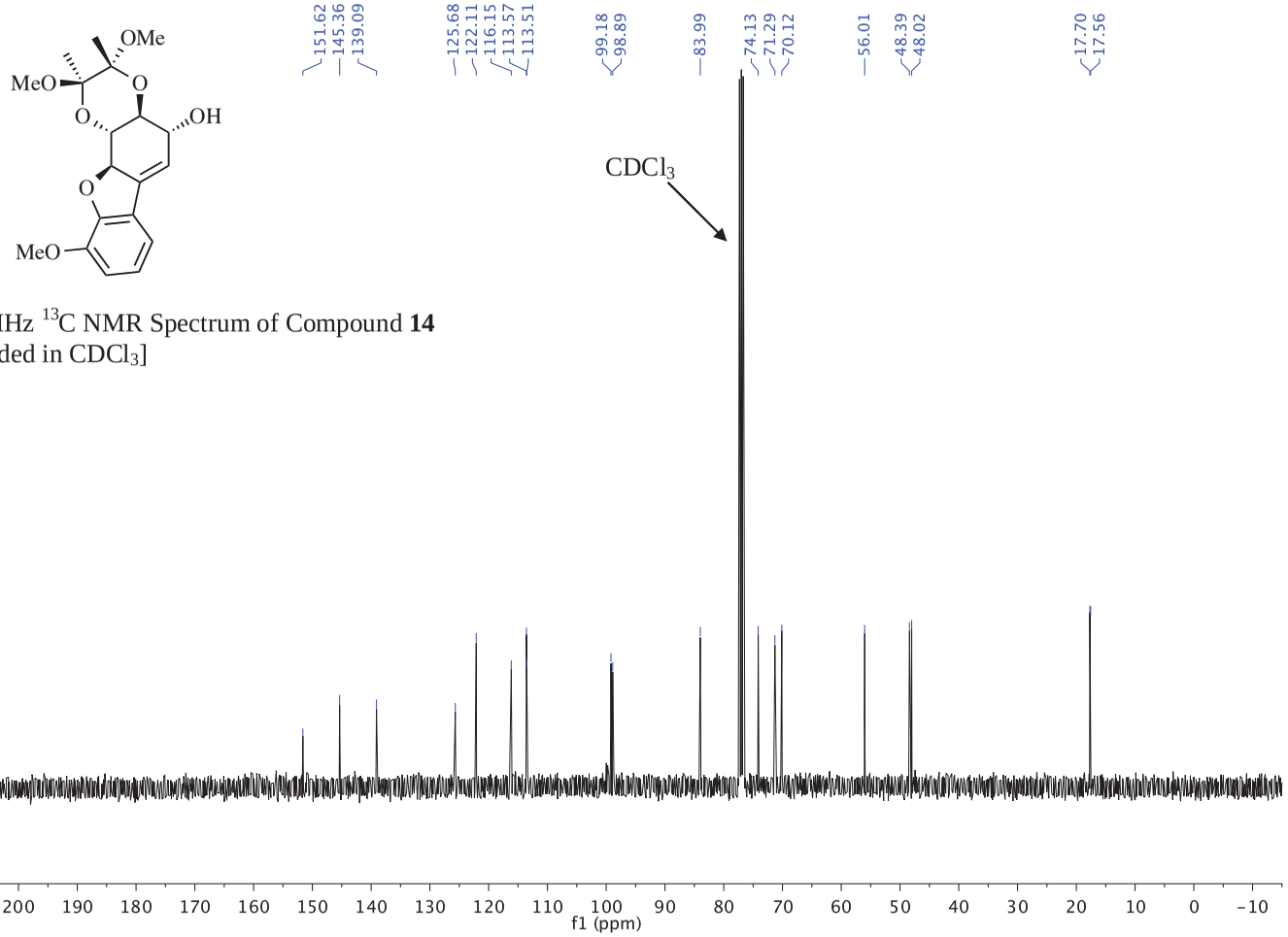
400 MHz ^{1}H NMR Spectrum of Compound **13**
[recorded in CD_3OD]



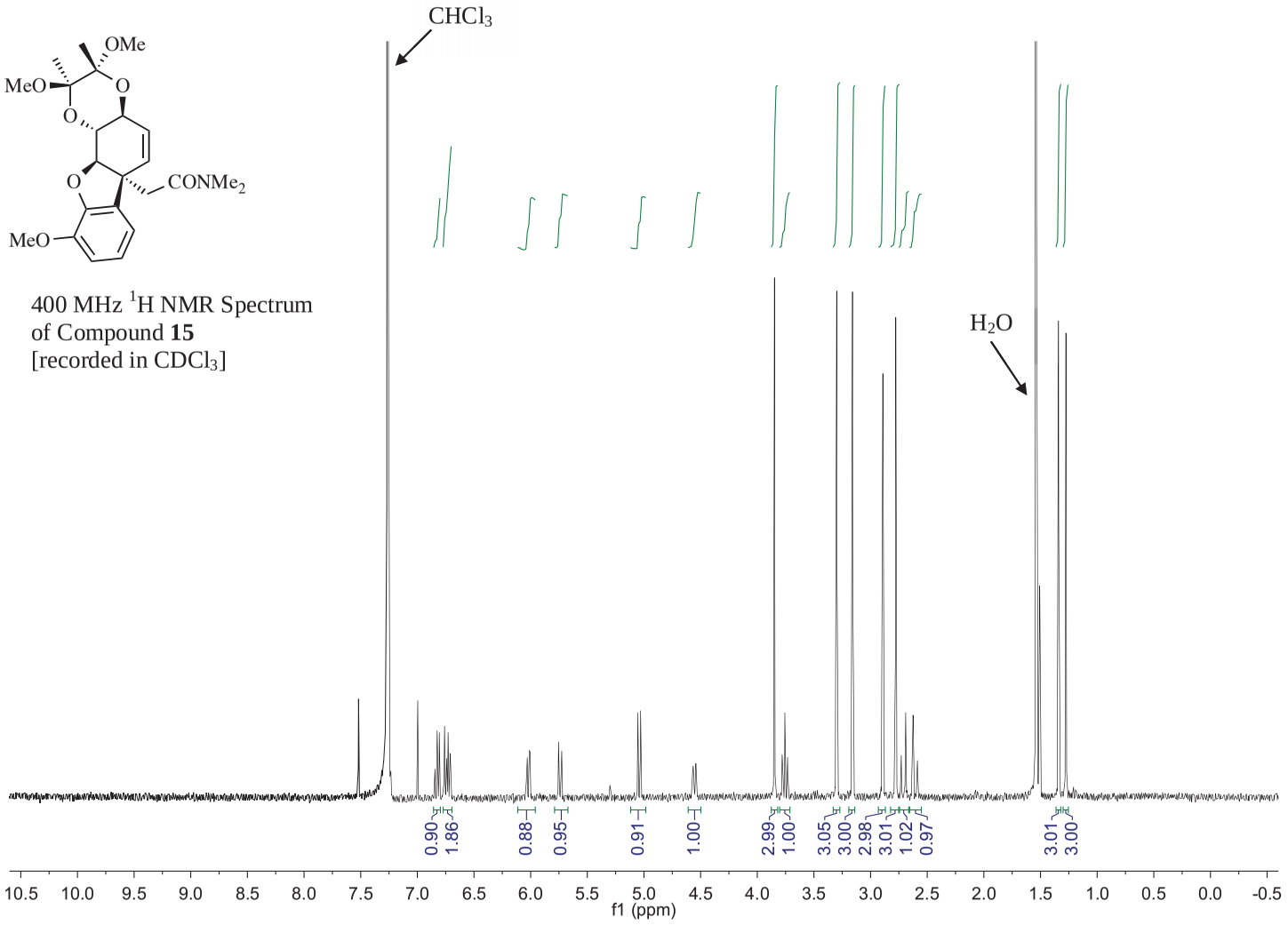
100 MHz ^{13}C NMR Spectrum of Compound **13**
[recorded in CD_3OD]



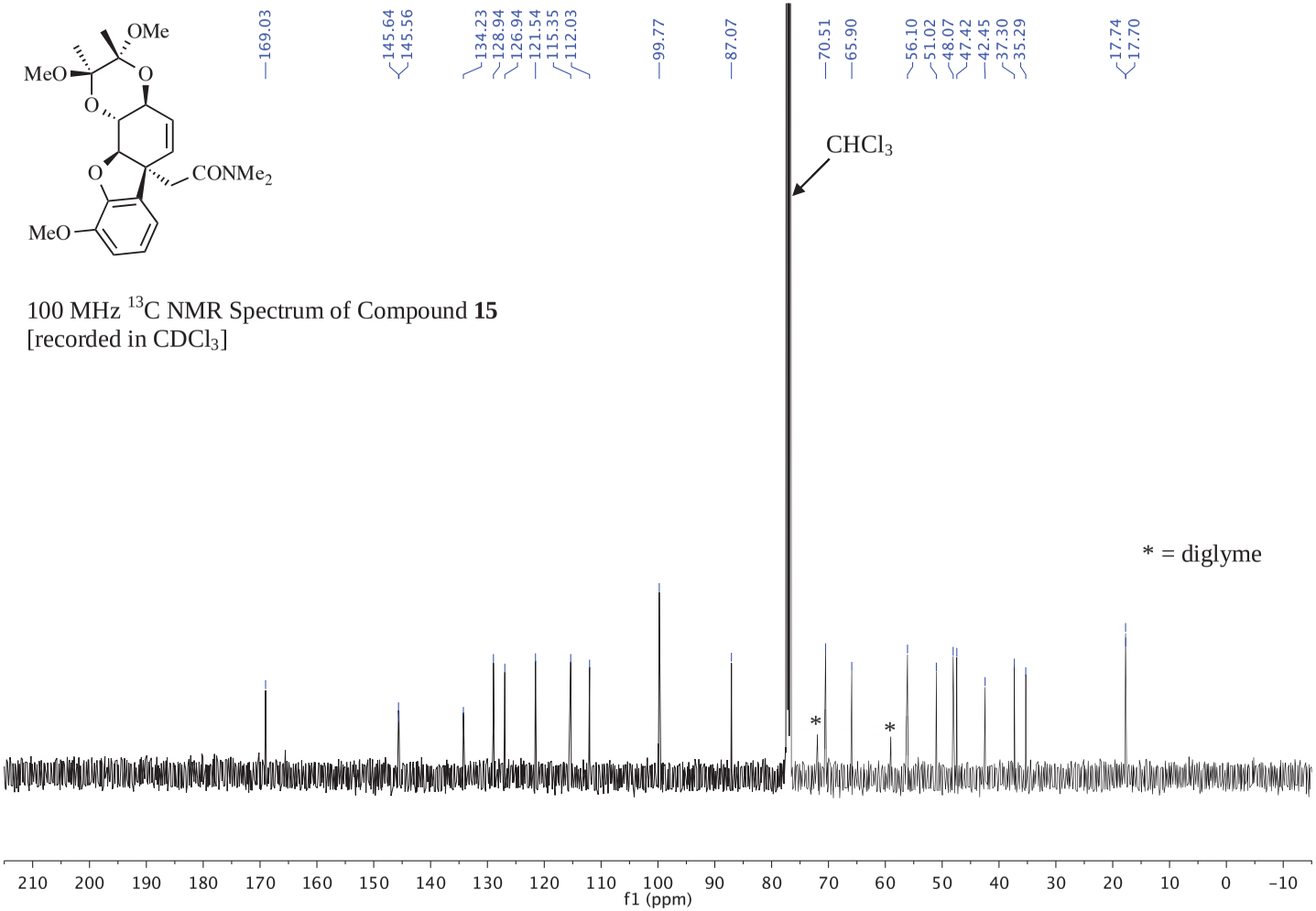
400 MHz ^{1}H NMR Spectrum of Compound **14**
[recorded in $CDCl_3$]



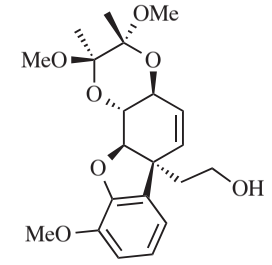
100 MHz ^{13}C NMR Spectrum of Compound **14**
[recorded in $CDCl_3$]



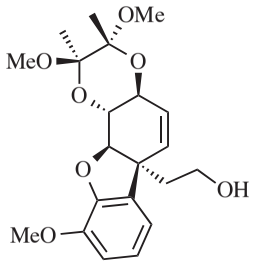
400 MHz ^{1}H NMR Spectrum
of Compound **15**
[recorded in $CDCl_3$]



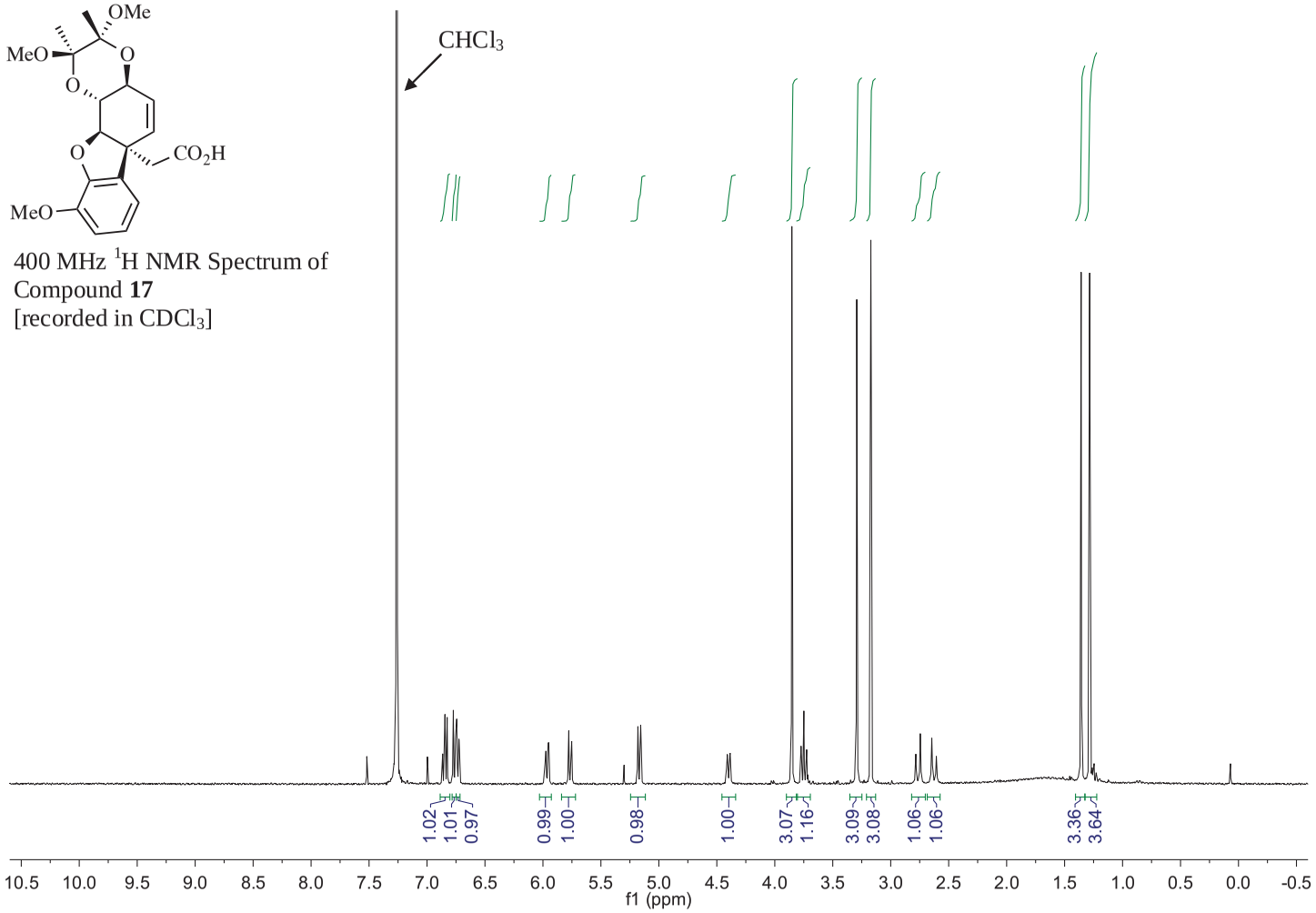
100 MHz ^{13}C NMR Spectrum of Compound **15**
[recorded in $CDCl_3$]



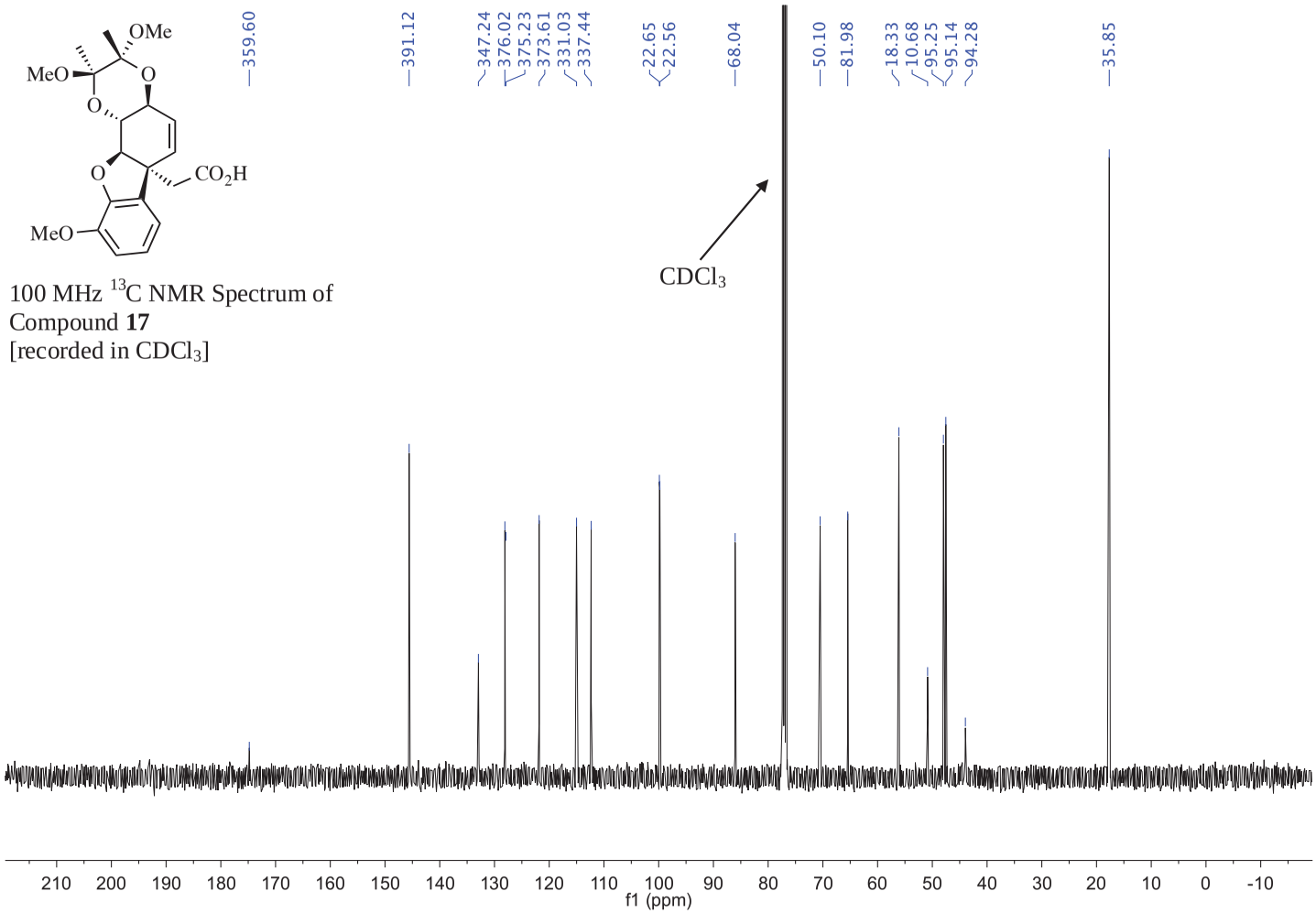
400 MHz ^{1}H NMR Spectrum of
Compound **16** [recorded in $CDCl_3$]



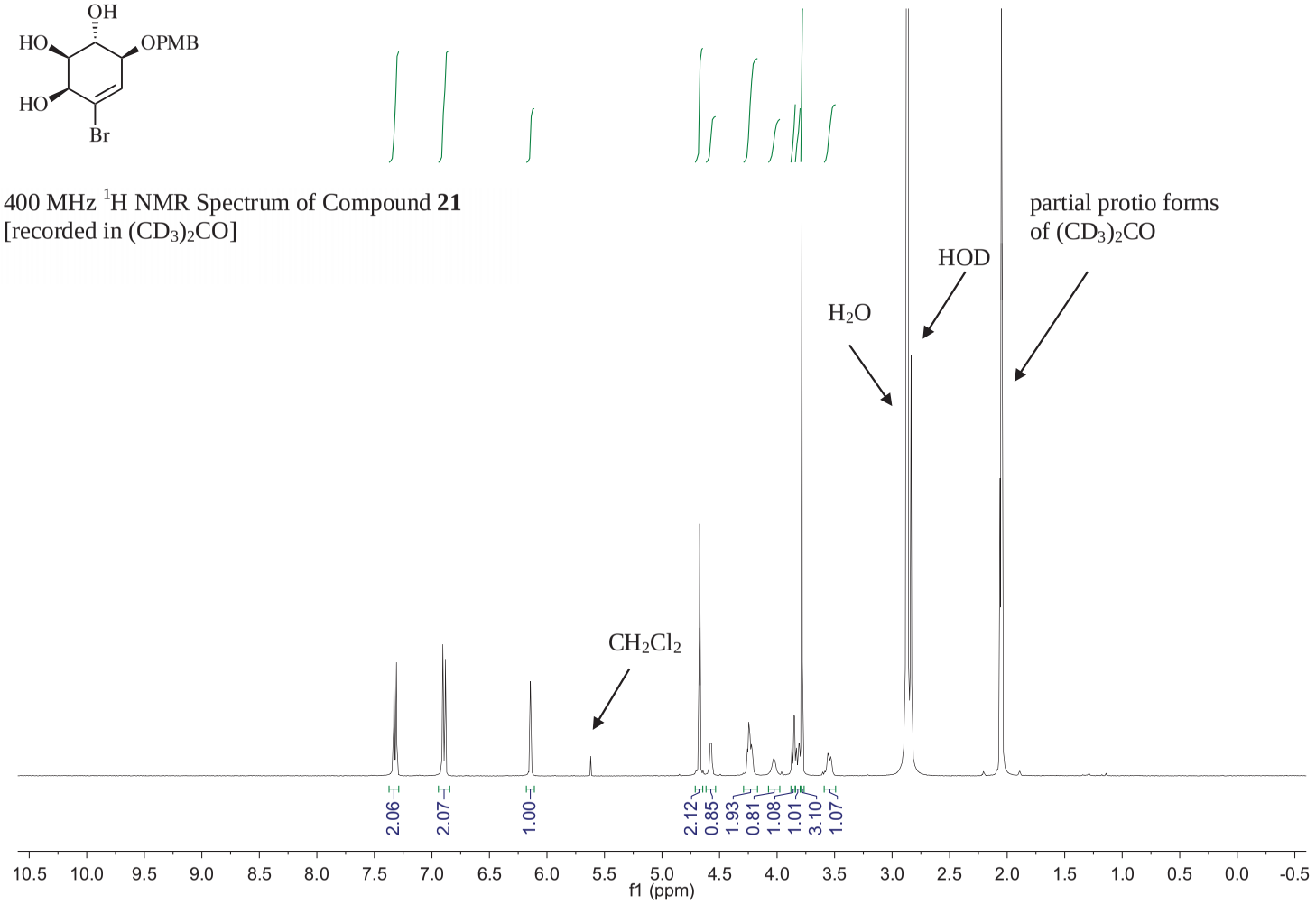
100 MHz ^{13}C NMR Spectrum of
Compound **16**
[recorded in $CDCl_3$]

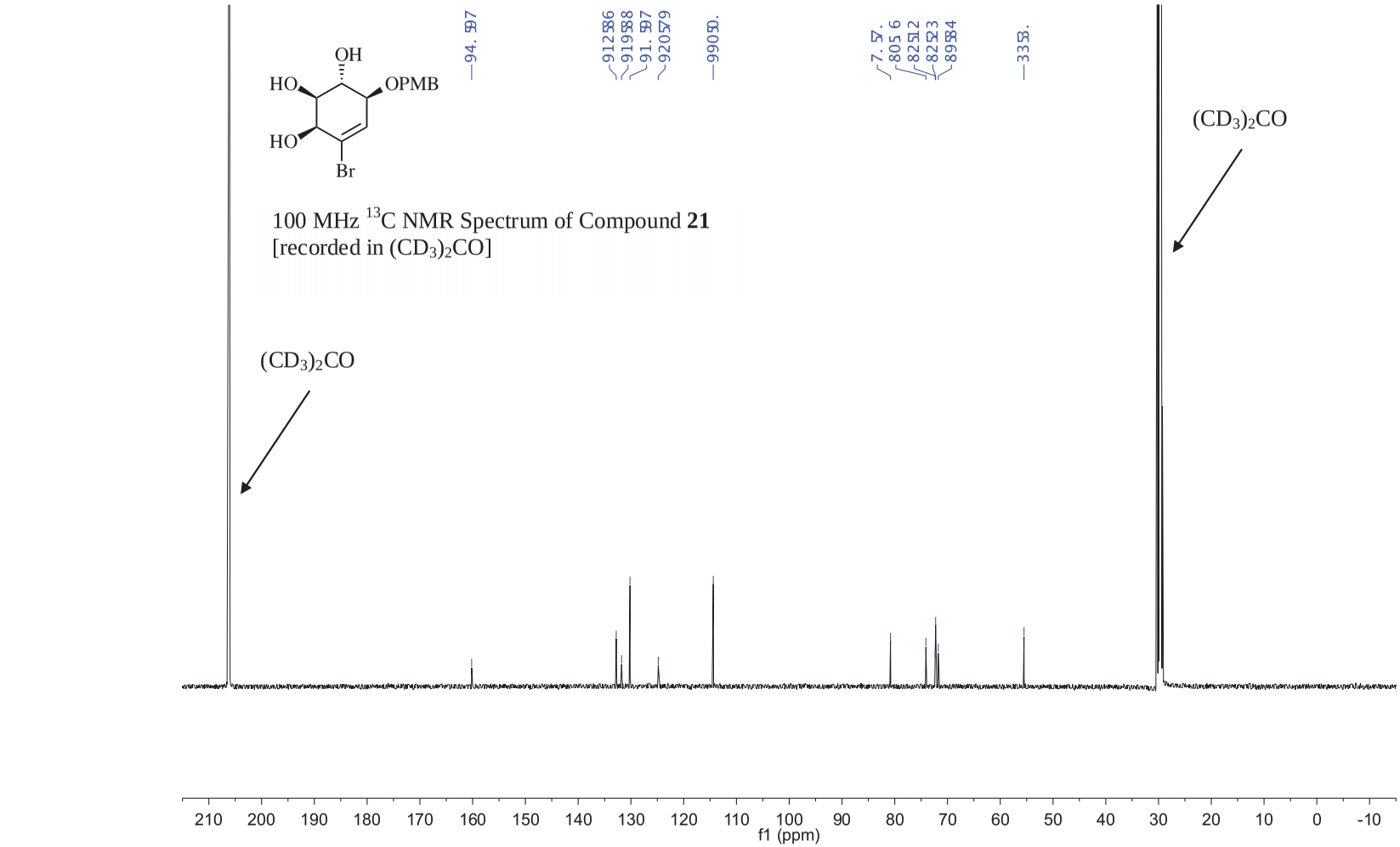


400 MHz ^{1}H NMR Spectrum of Compound **17** [recorded in $CDCl_3$]



100 MHz ^{13}C NMR Spectrum of
Compound **17**
[recorded in $CDCl_3$]

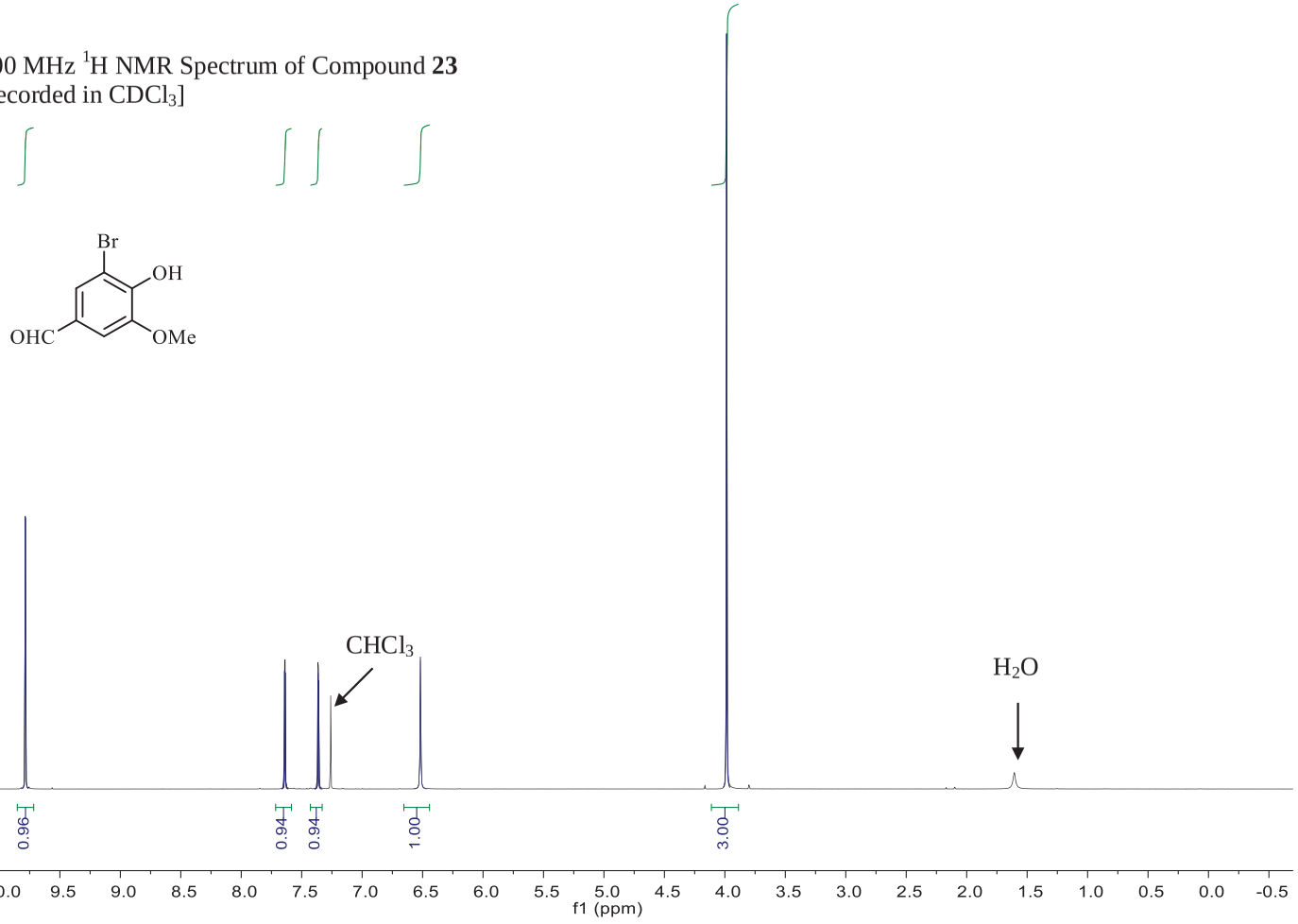

OH
HO
OPMB
HO
Br
400 MHz ^{1}H NMR Spectrum of Compound **21**
[recorded in $(CD_3)_2CO$]
partial protio forms
of $(CD_3)_2CO$
HOD
H_2O
CH_2Cl_2
2.06
2.07
1.00
2.12
0.85
1.93
0.81
1.08
1.01
3.10
1.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

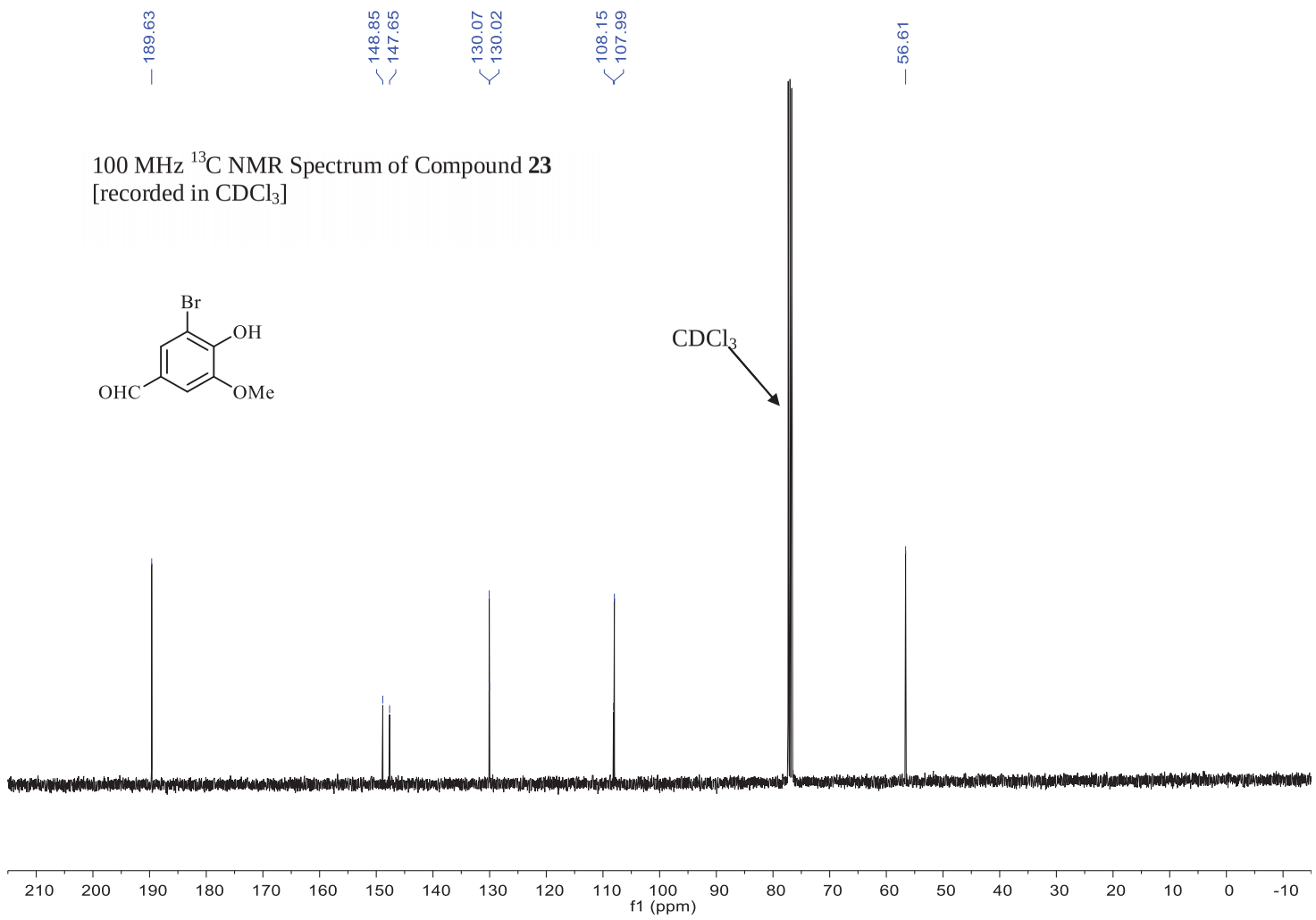


100 MHz ^{13}C NMR Spectrum of Compound **21**
[recorded in $(CD_3)_2CO$]

131

400 MHz ^{1}H NMR Spectrum of Compound **23**
[recorded in $CDCl_3$]

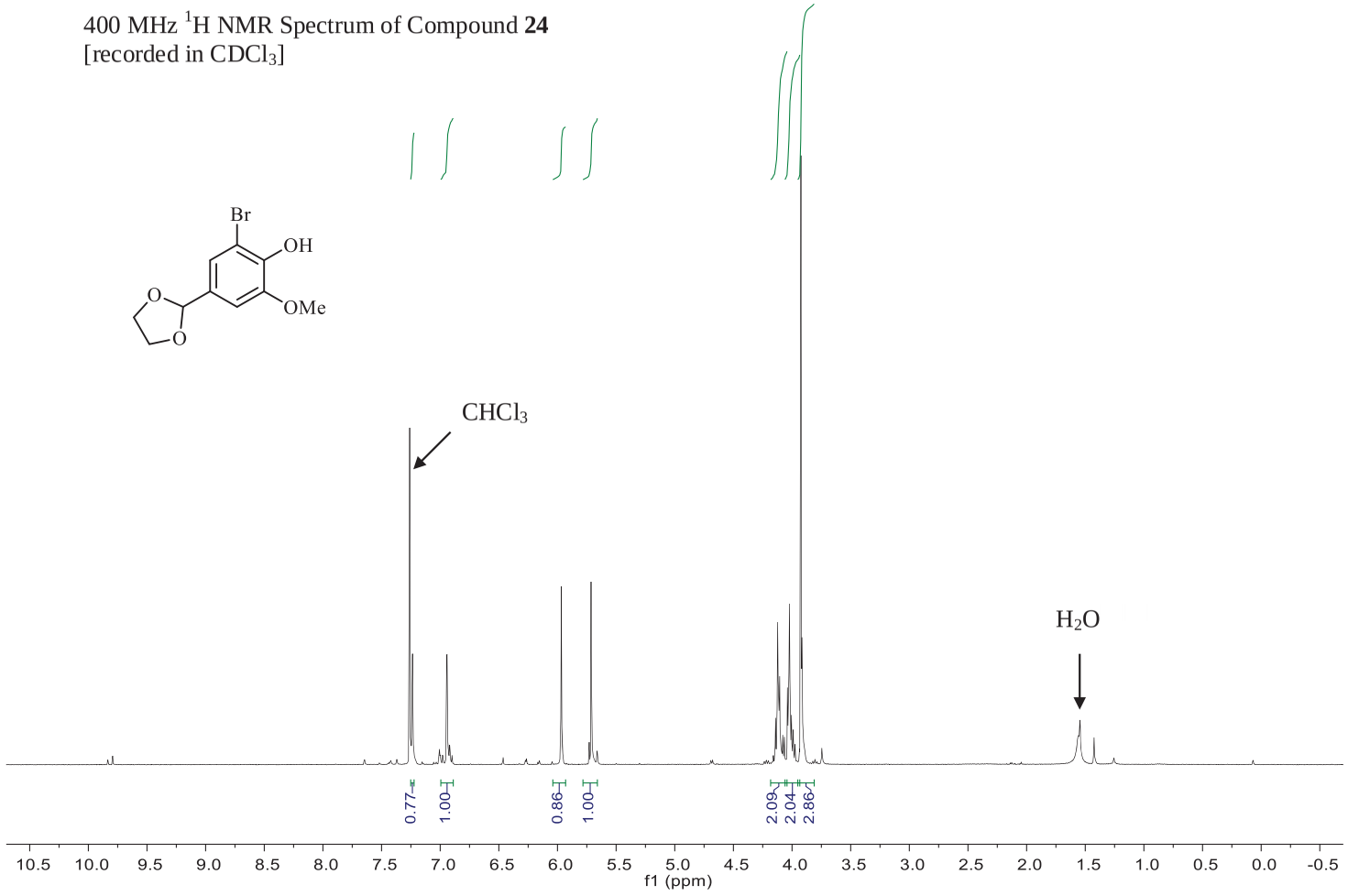




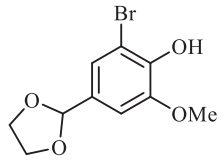
100 MHz ^{13}C NMR Spectrum of Compound **23**
[recorded in $CDCl_3$]

133

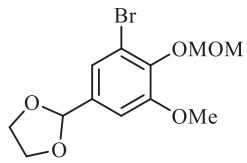
400 MHz ^{1}H NMR Spectrum of Compound **24**
[recorded in $CDCl_3$]



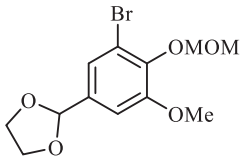
100 MHz ^{13}C NMR Spectrum of Compound **24**
[recorded in $CDCl_3$]



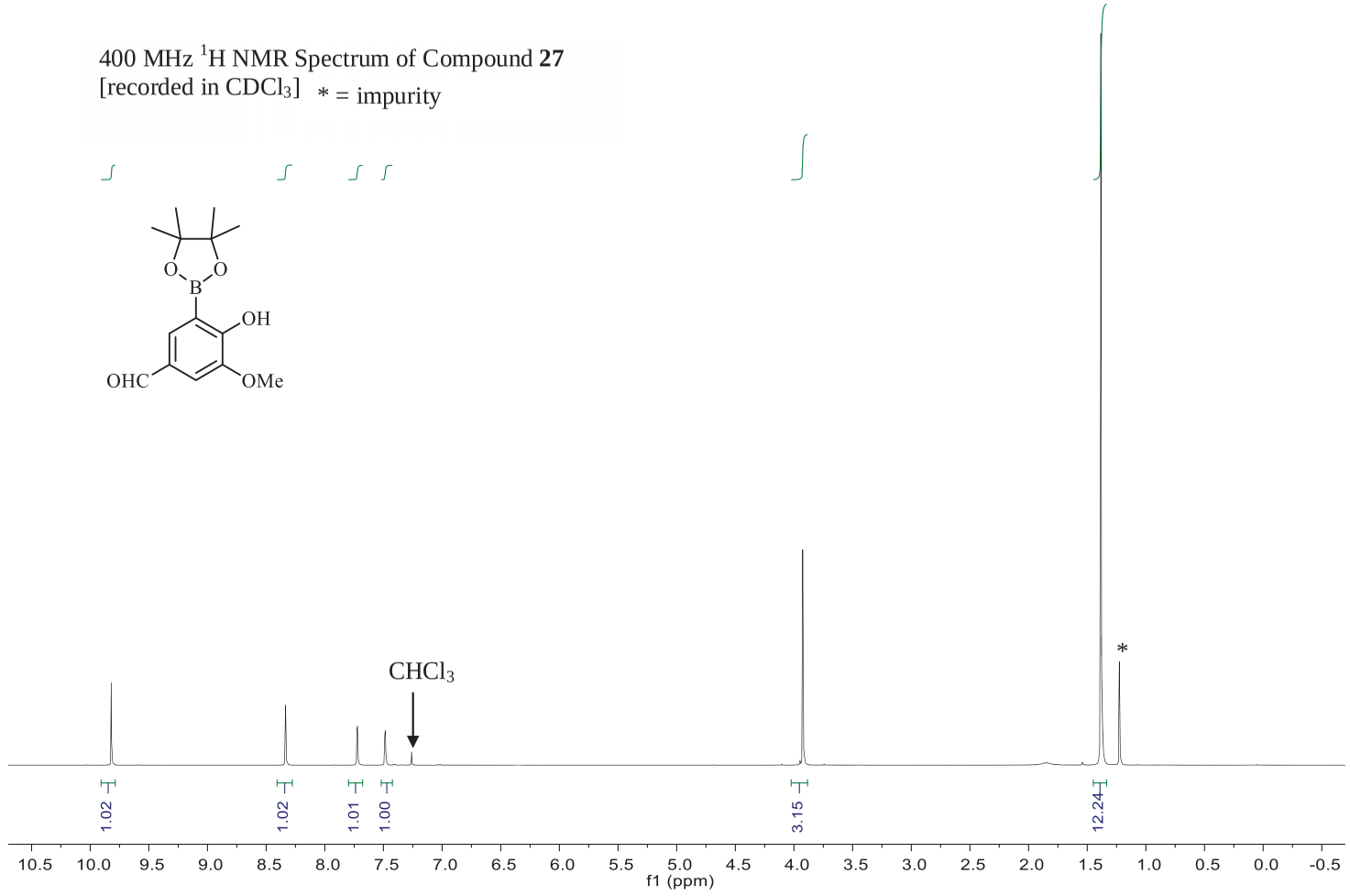
400 MHz ^{1}H NMR Spectrum of Compound **25**
[recorded in $CDCl_3$]



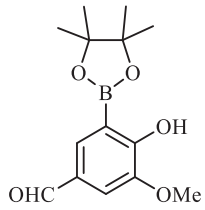
100 MHz ^{13}C NMR Spectrum of Compound **25**
[recorded in $CDCl_3$]



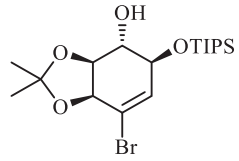
400 MHz ^{1}H NMR Spectrum of Compound **27**
[recorded in $CDCl_3$] * = impurity



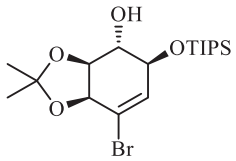
100 MHz ^{13}C NMR Spectrum of Compound **27**
[recorded in $CDCl_3$]



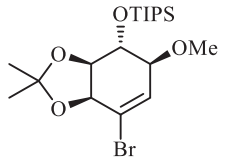
400 MHz ^{1}H NMR Spectrum of Compound **29**
[recorded in $CDCl_3$] * = minor regioisomer



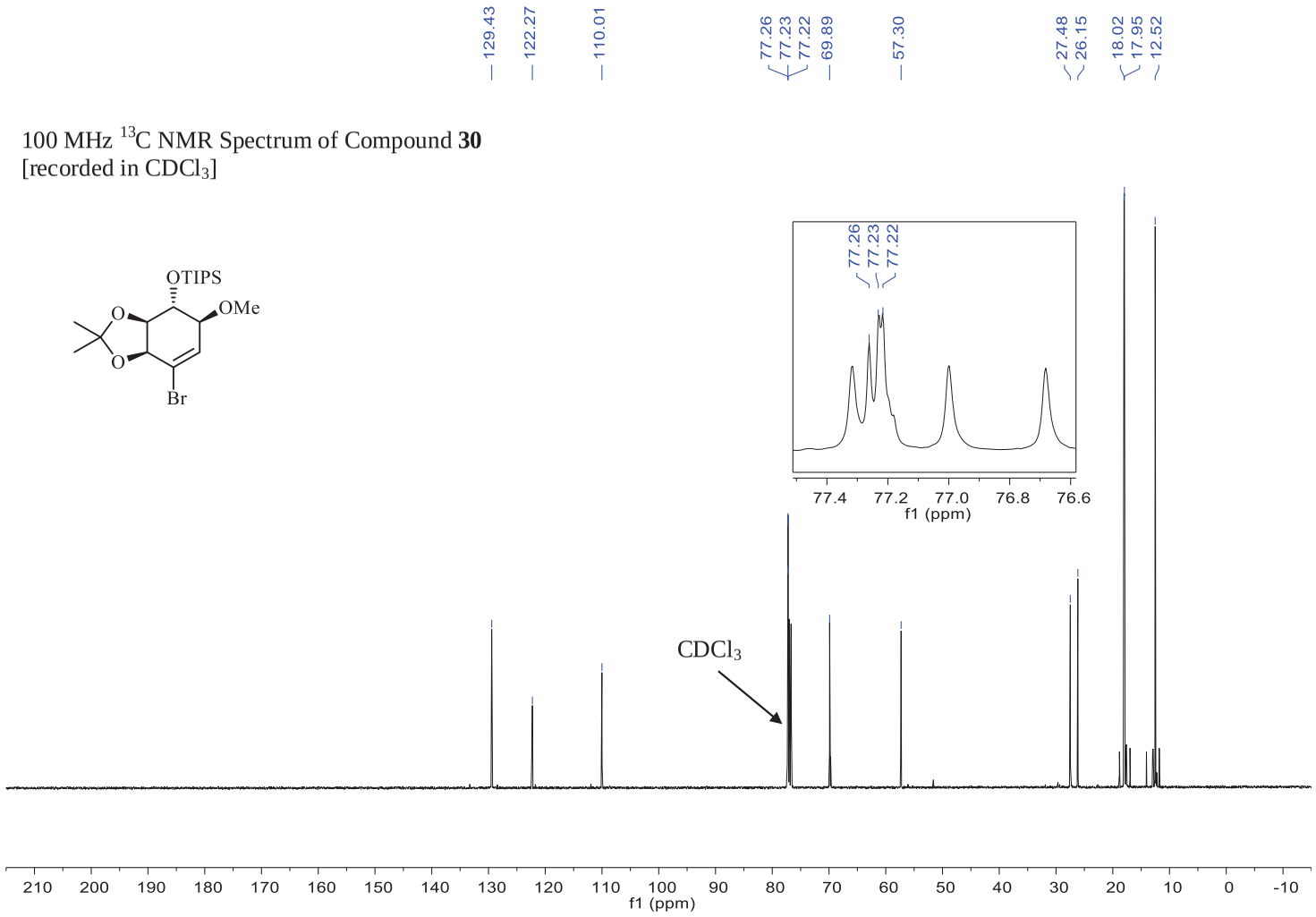
100 MHz ^{13}C NMR Spectrum of Compound **29**
[recorded in $CDCl_3$] * = minor regioisomer



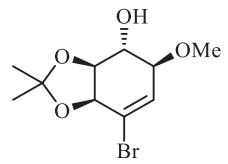
400 MHz ^{1}H NMR Spectrum of Compound **30**
[recorded in $CDCl_3$]



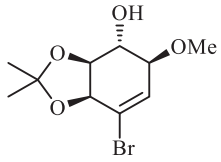
100 MHz ^{13}C NMR Spectrum of Compound **30**
[recorded in $CDCl_3$]



400 MHz ^{1}H NMR Spectrum of Compound **31**
[recorded in $CDCl_3$]

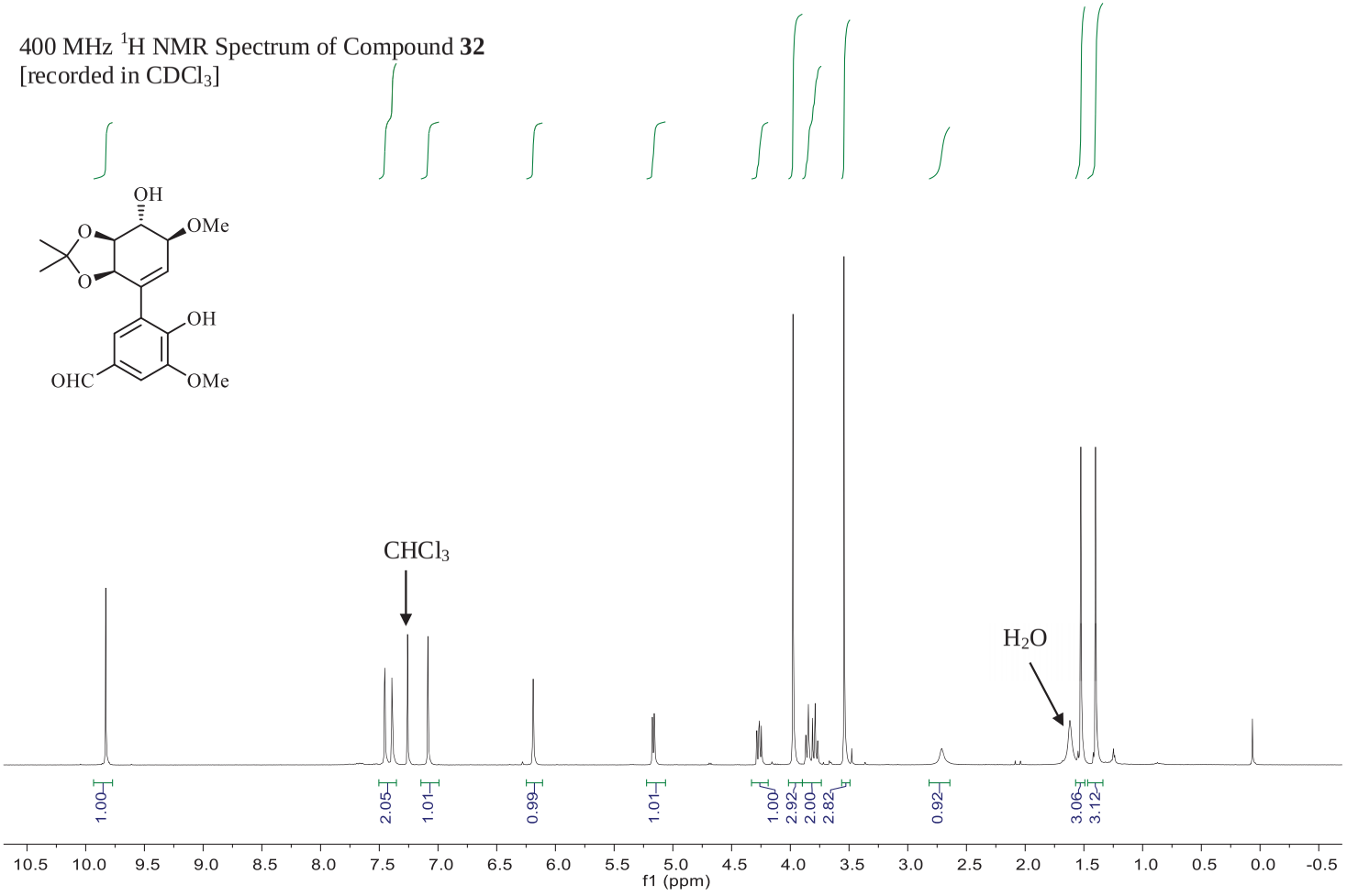


100 MHz ^{13}C NMR Spectrum of Compound **31**
[recorded in $CDCl_3$]

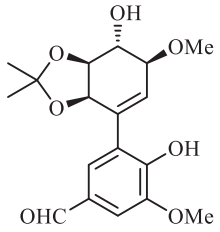


145

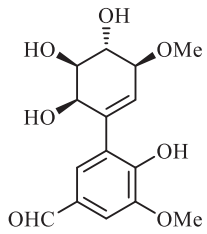
400 MHz ^{1}H NMR Spectrum of Compound **32**
[recorded in $CDCl_3$]

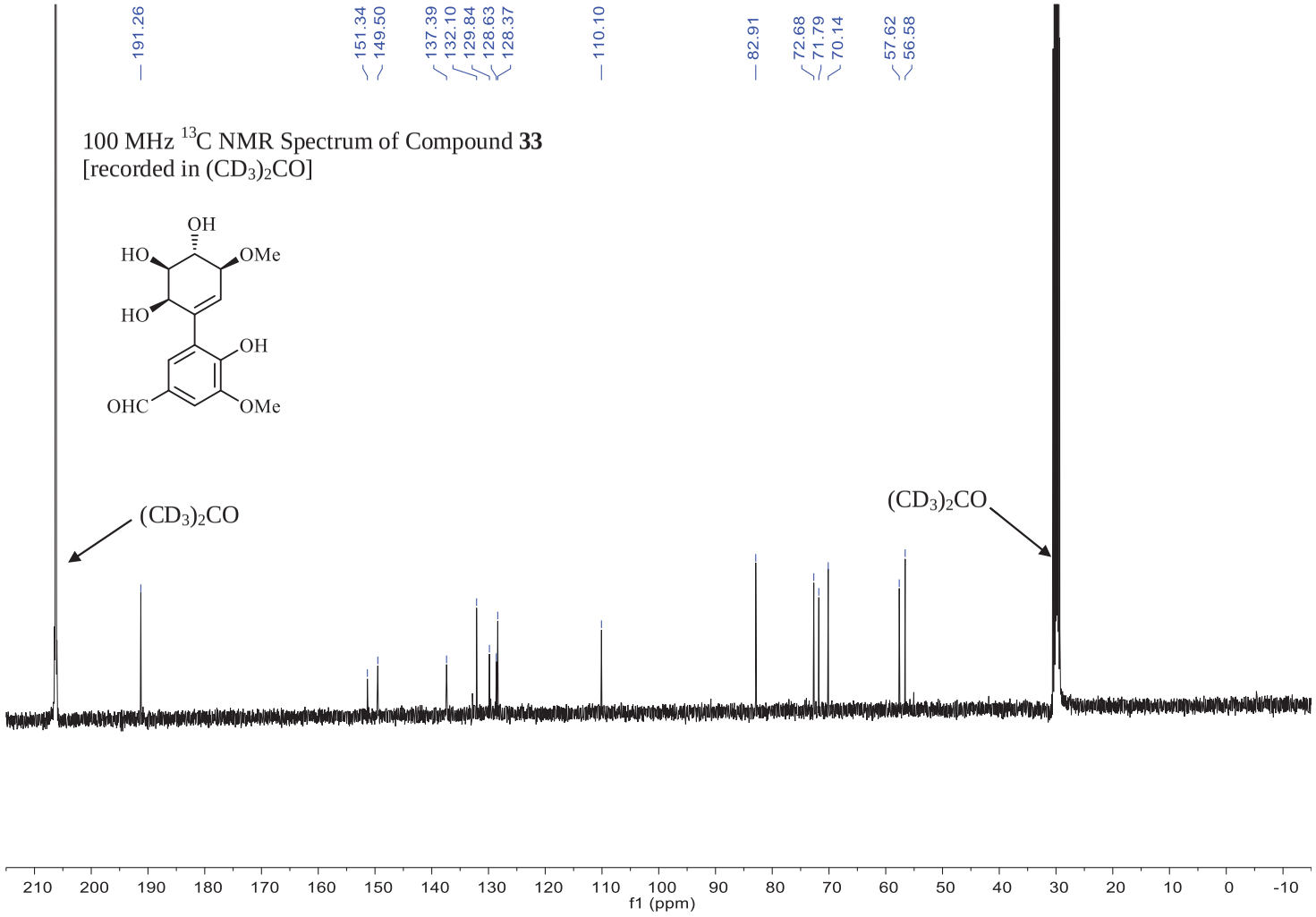


100 MHz ^{13}C NMR Spectrum of Compound **32**
[recorded in $CDCl_3$]

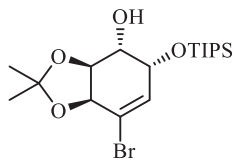


400 MHz ^{1}H NMR Spectrum of Compound **33**
[recorded in $(CD_3)_2CO$]

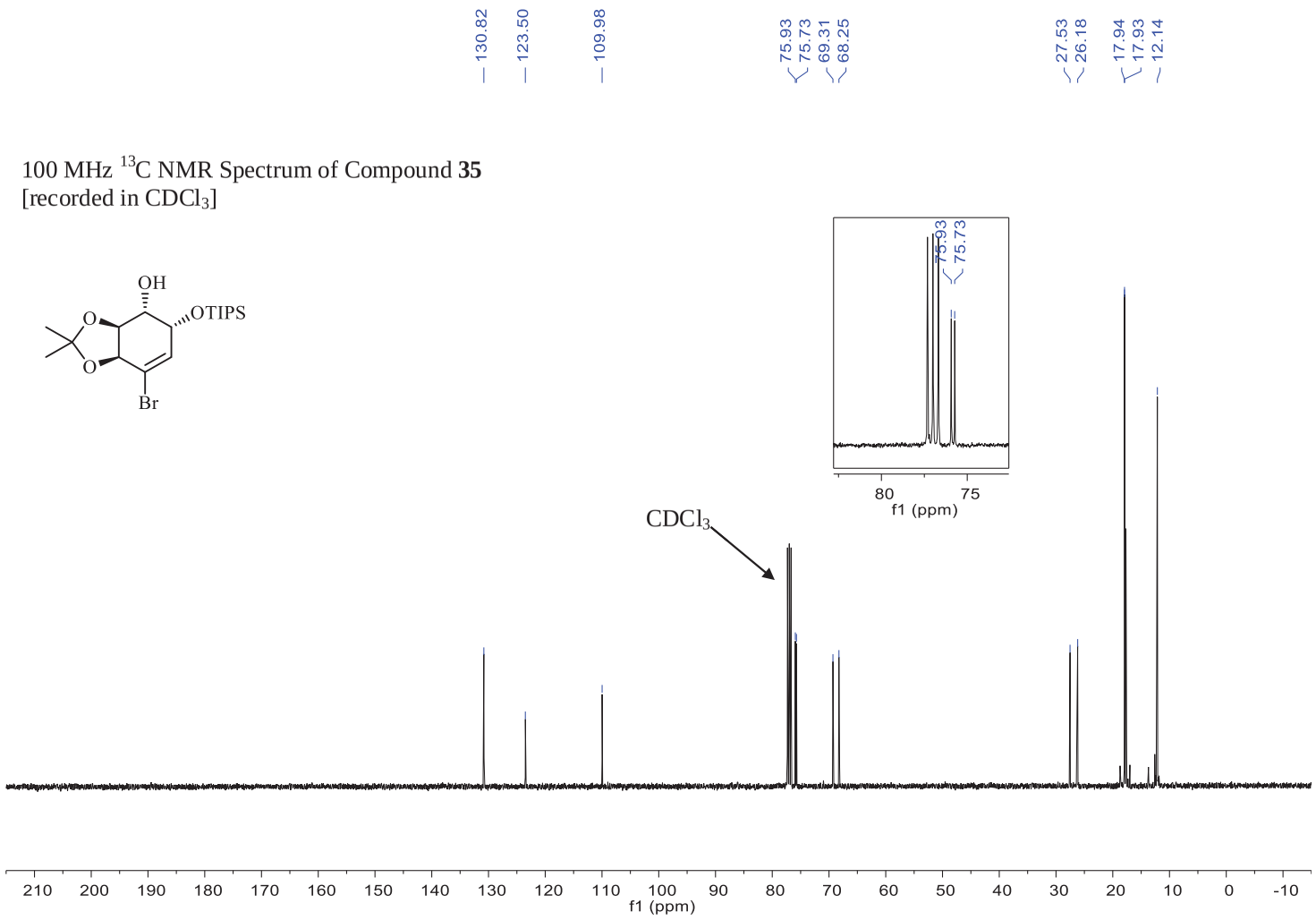



191.26
151.34
149.50
137.39
132.10
129.84
128.63
128.37
110.10
82.91
72.68
71.79
70.14
57.62
56.58
100 MHz 13C NMR Spectrum of Compound 33
[recorded in (CD3)2CO]
OH
HO
OMe
HO
OH
OHC
OMe
(CD3)2CO
(CD3)2CO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

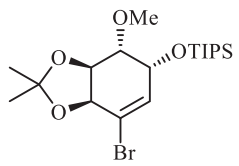
400 MHz ^{1}H NMR Spectrum of Compound **35**
[recorded in $CDCl_3$]



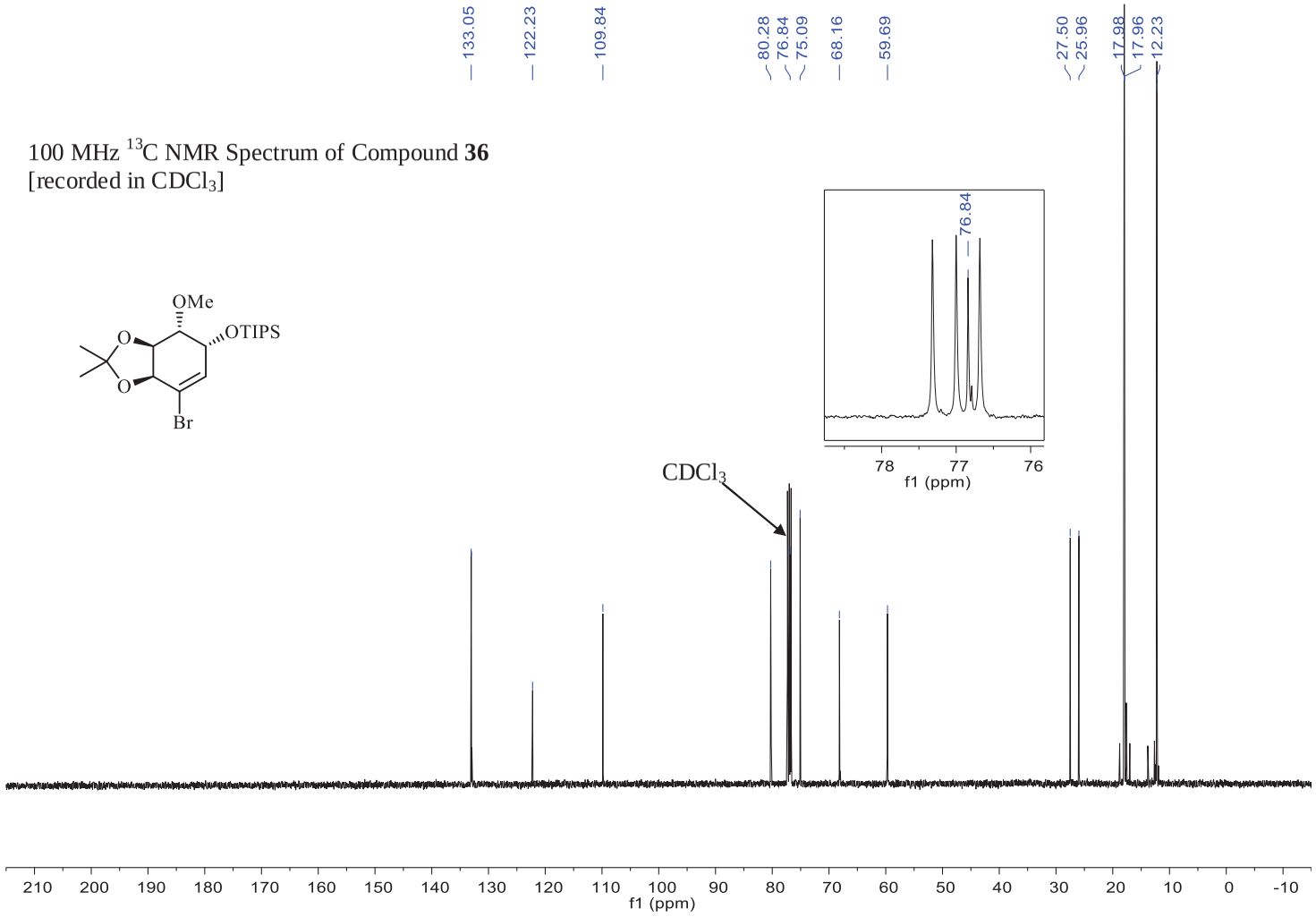
100 MHz ^{13}C NMR Spectrum of Compound **35**
[recorded in $CDCl_3$]



400 MHz ^{1}H NMR Spectrum of Compound **36**
[recorded in $CDCl_3$]

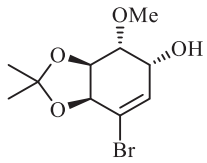


100 MHz ^{13}C NMR Spectrum of Compound **36**
[recorded in $CDCl_3$]

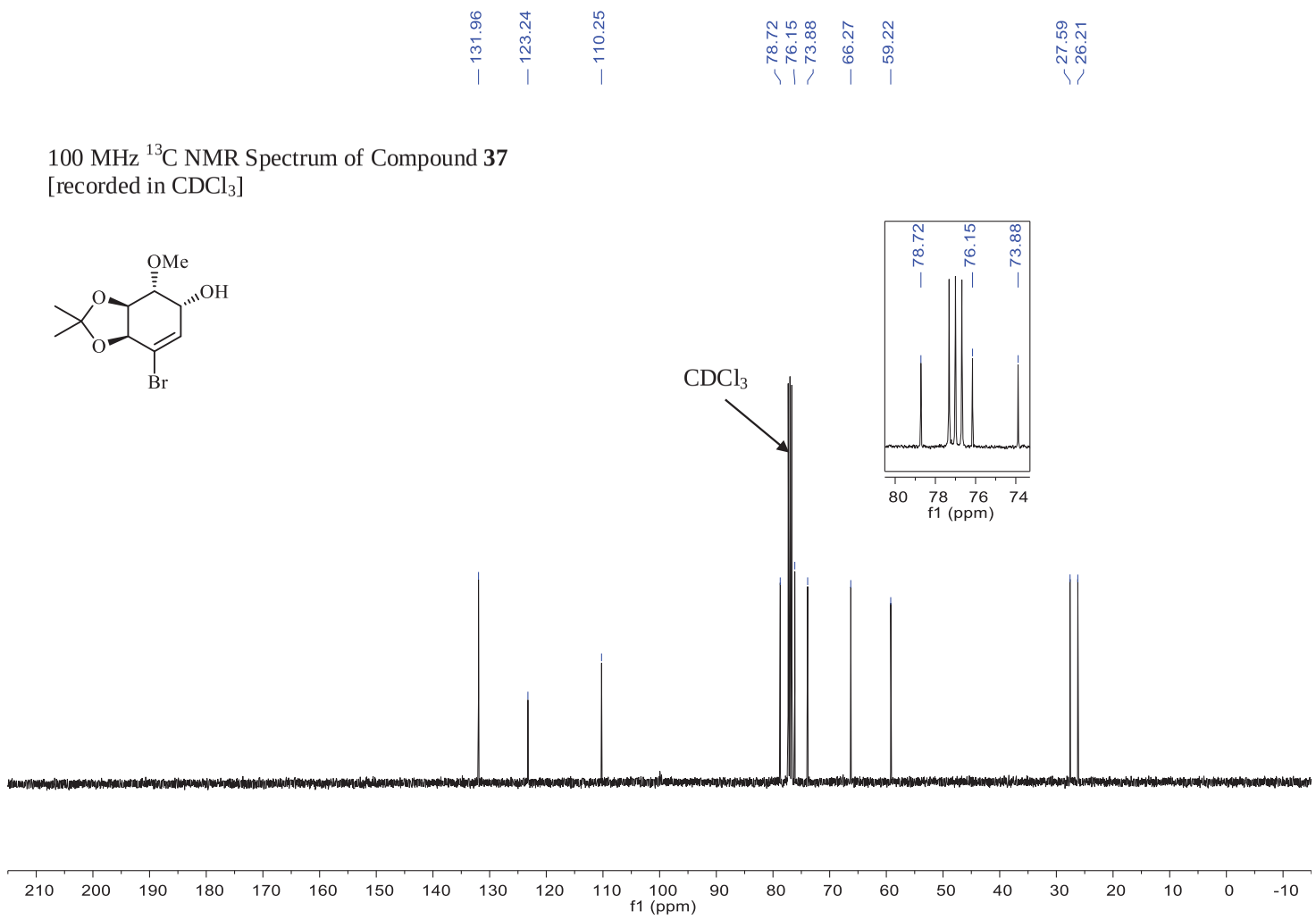


153

400 MHz ^{1}H NMR Spectrum of Compound **37**
[recorded in $CDCl_3$]

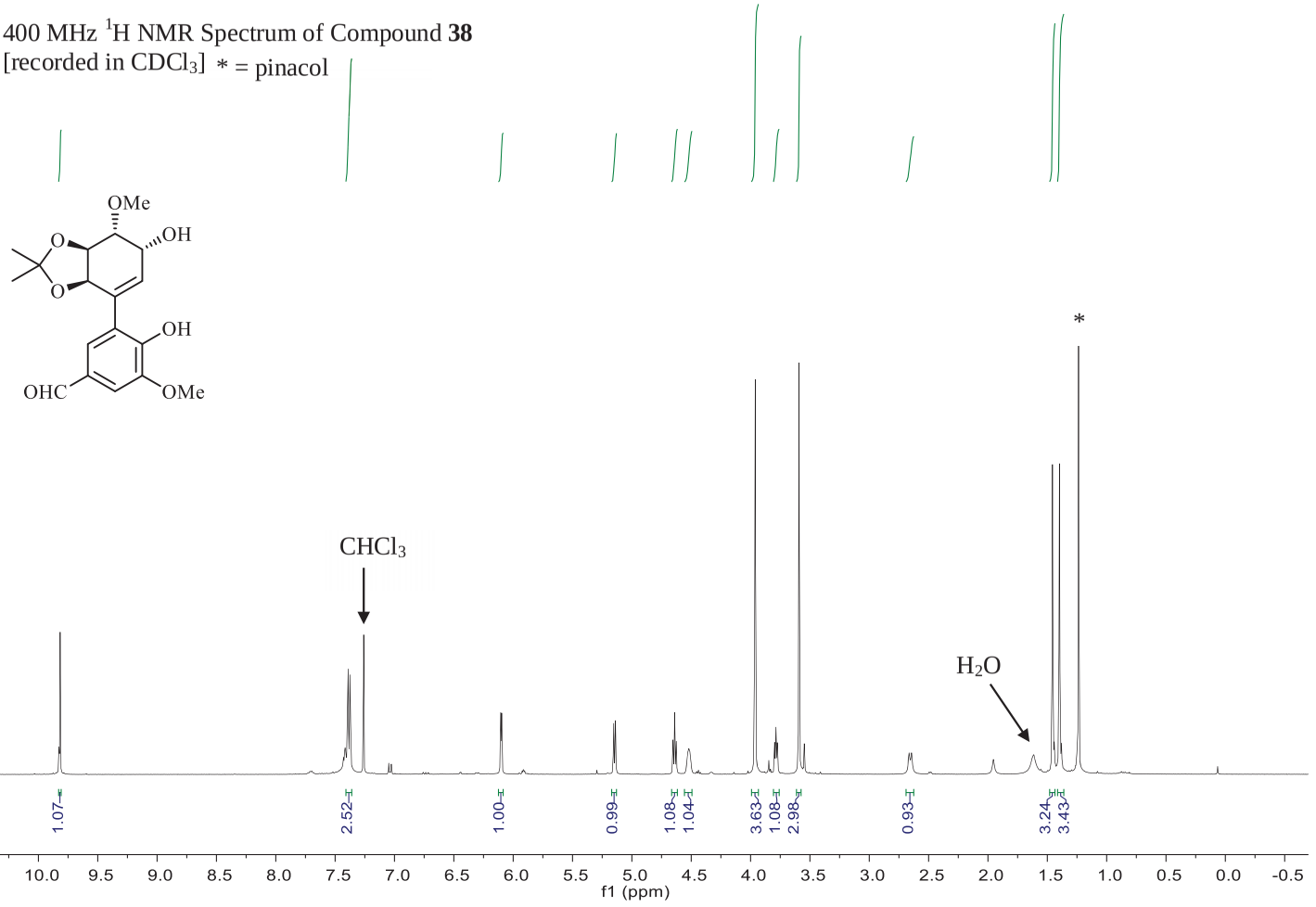


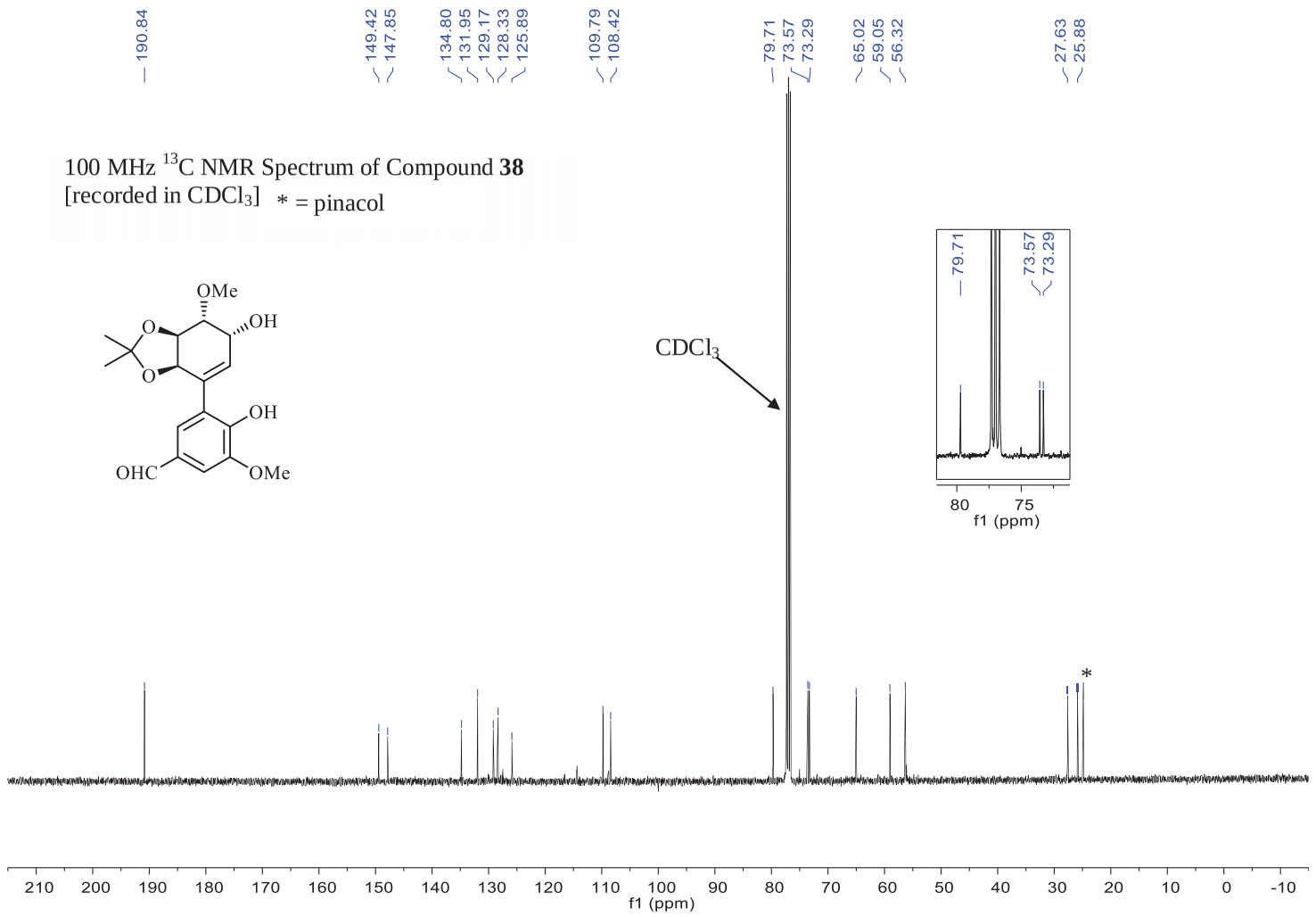
100 MHz ^{13}C NMR Spectrum of Compound **37**
[recorded in $CDCl_3$]



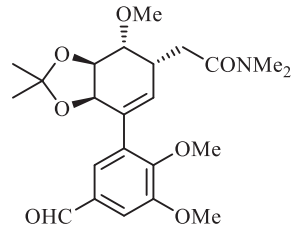
155

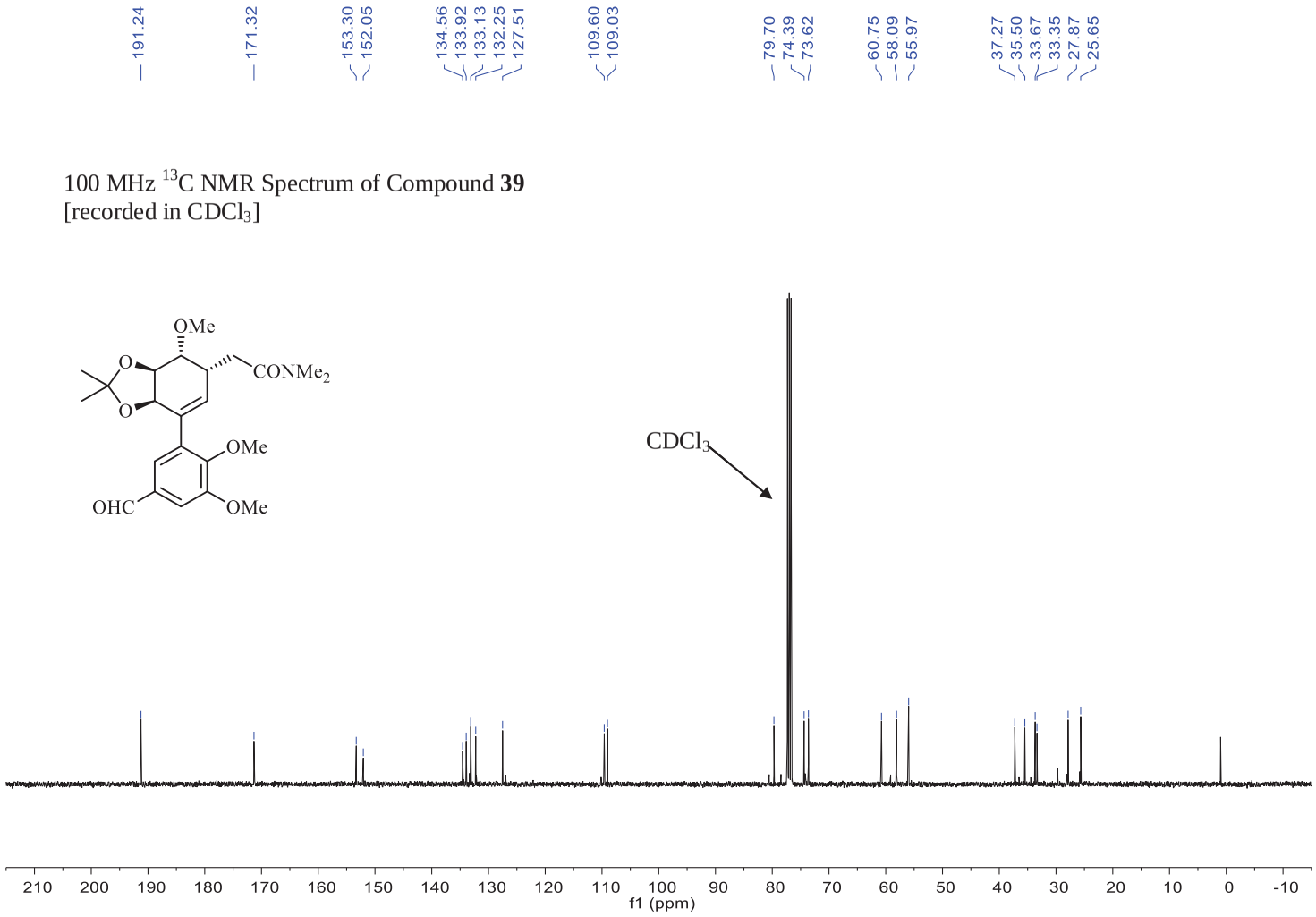
400 MHz ^{1}H NMR Spectrum of Compound **38**
[recorded in $CDCl_3$] * = pinacol




190.84
149.42
147.85
134.80
131.95
129.17
128.33
125.89
109.79
108.42
79.71
73.57
73.29
65.02
59.05
56.32
27.63
25.88
100 MHz 13C NMR Spectrum of Compound 38
[recorded in CDCl3] * = pinacol
OMe
OH
O
O
OH
OHC
OMe
CDCl3
*
80
75
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **39**
[recorded in $CDCl_3$]

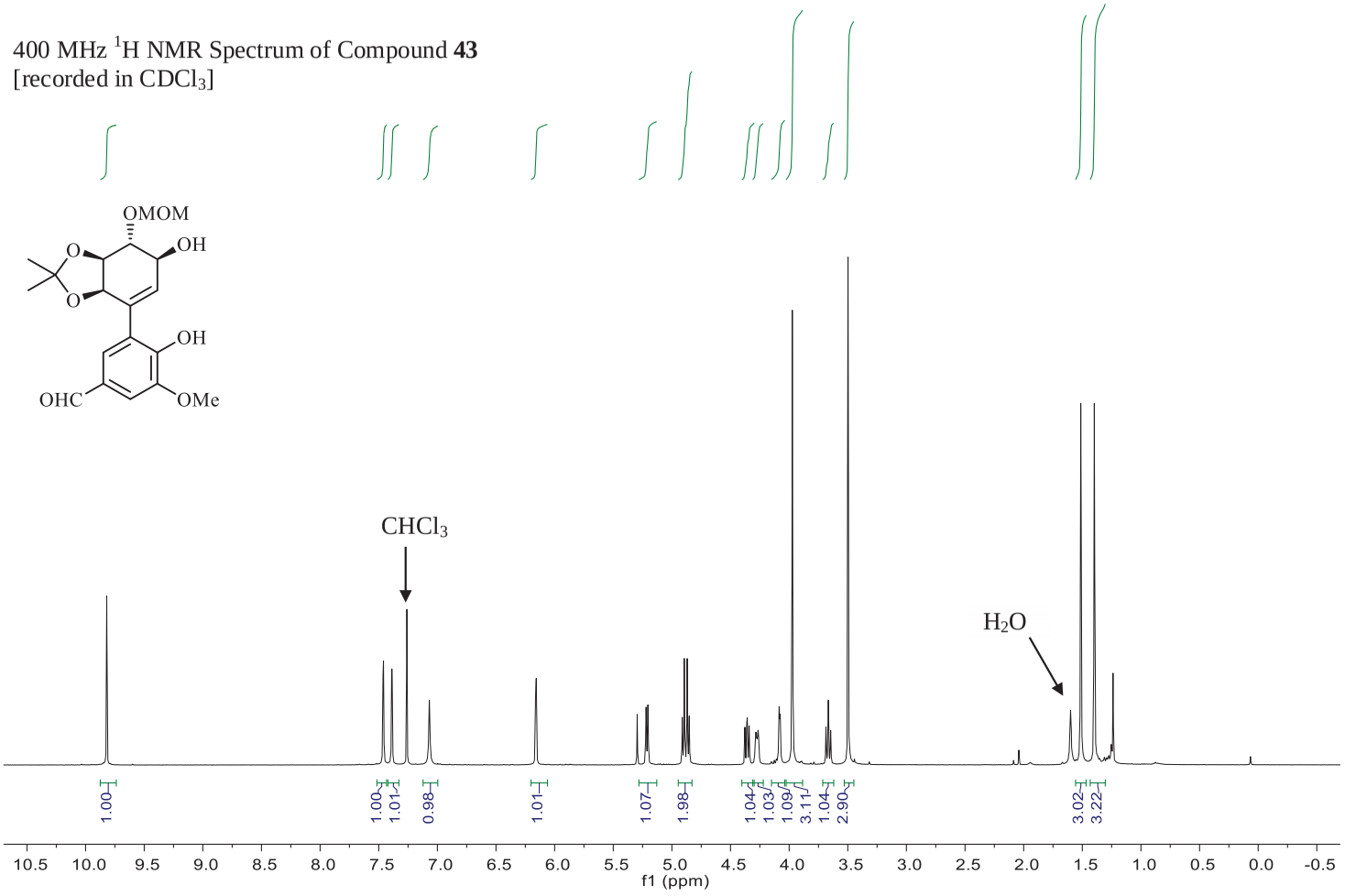




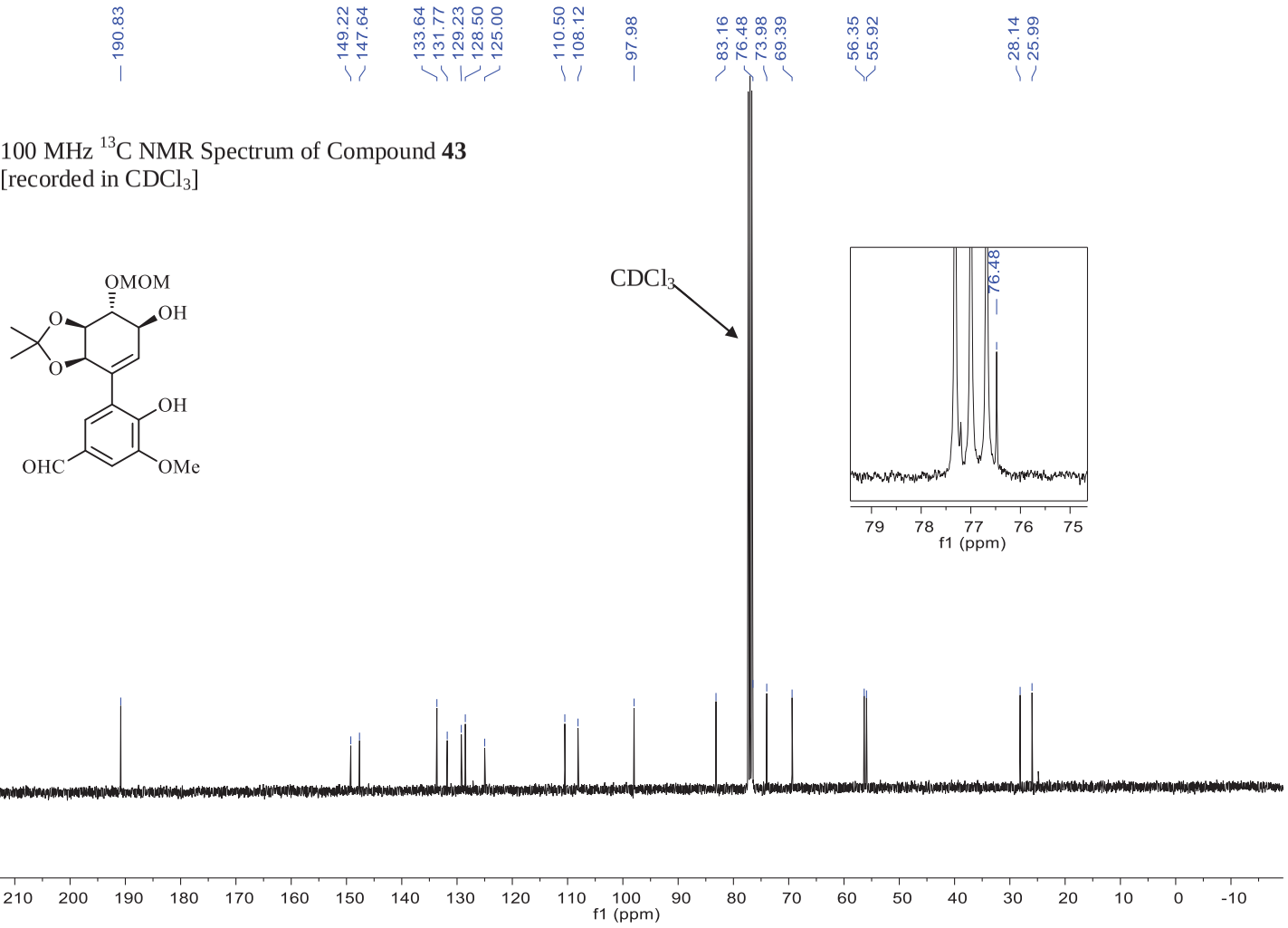
100 MHz ^{13}C NMR Spectrum of Compound **39**
[recorded in $CDCl_3$]

160

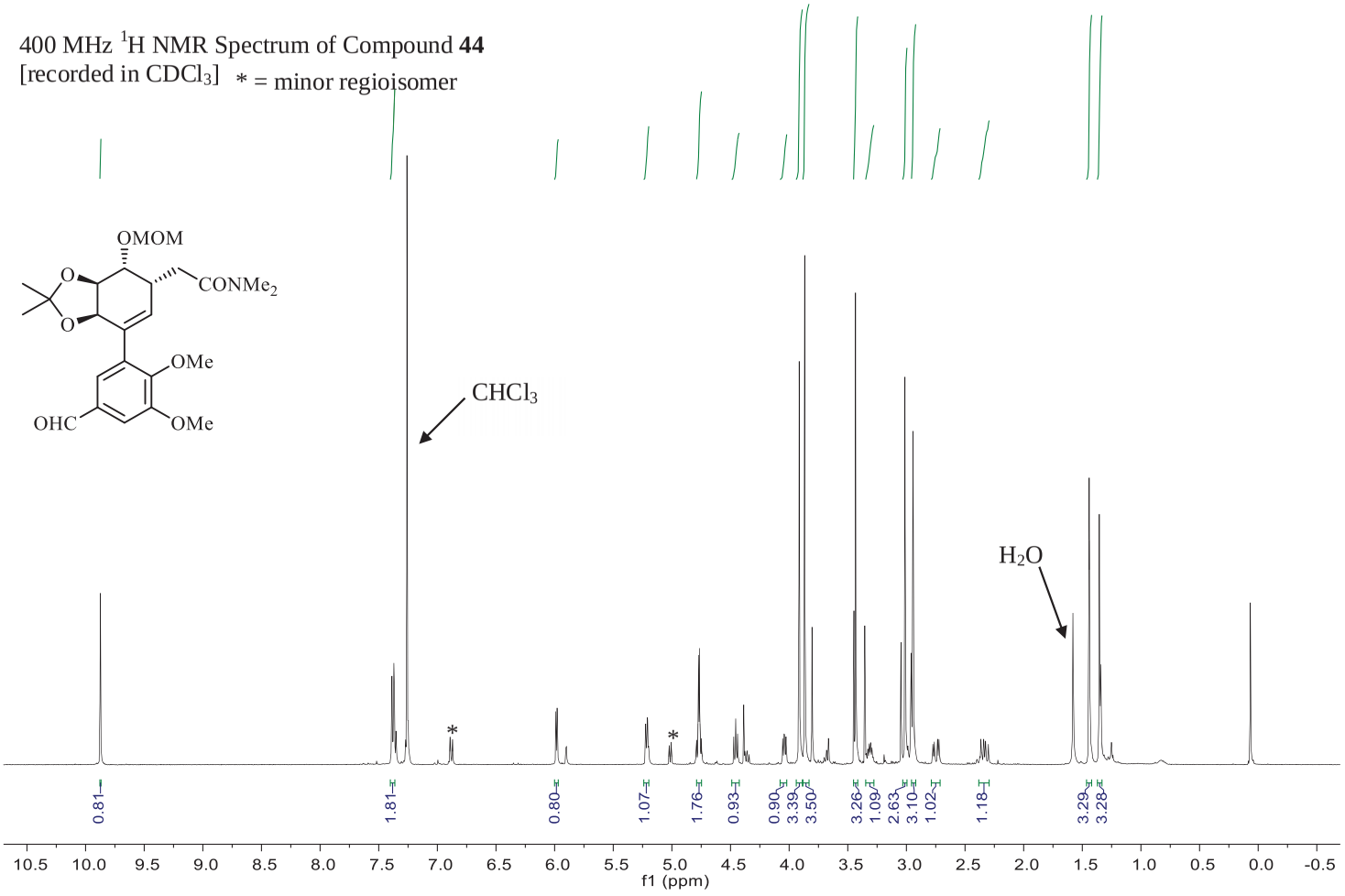
400 MHz ^{1}H NMR Spectrum of Compound **43**
[recorded in $CDCl_3$]



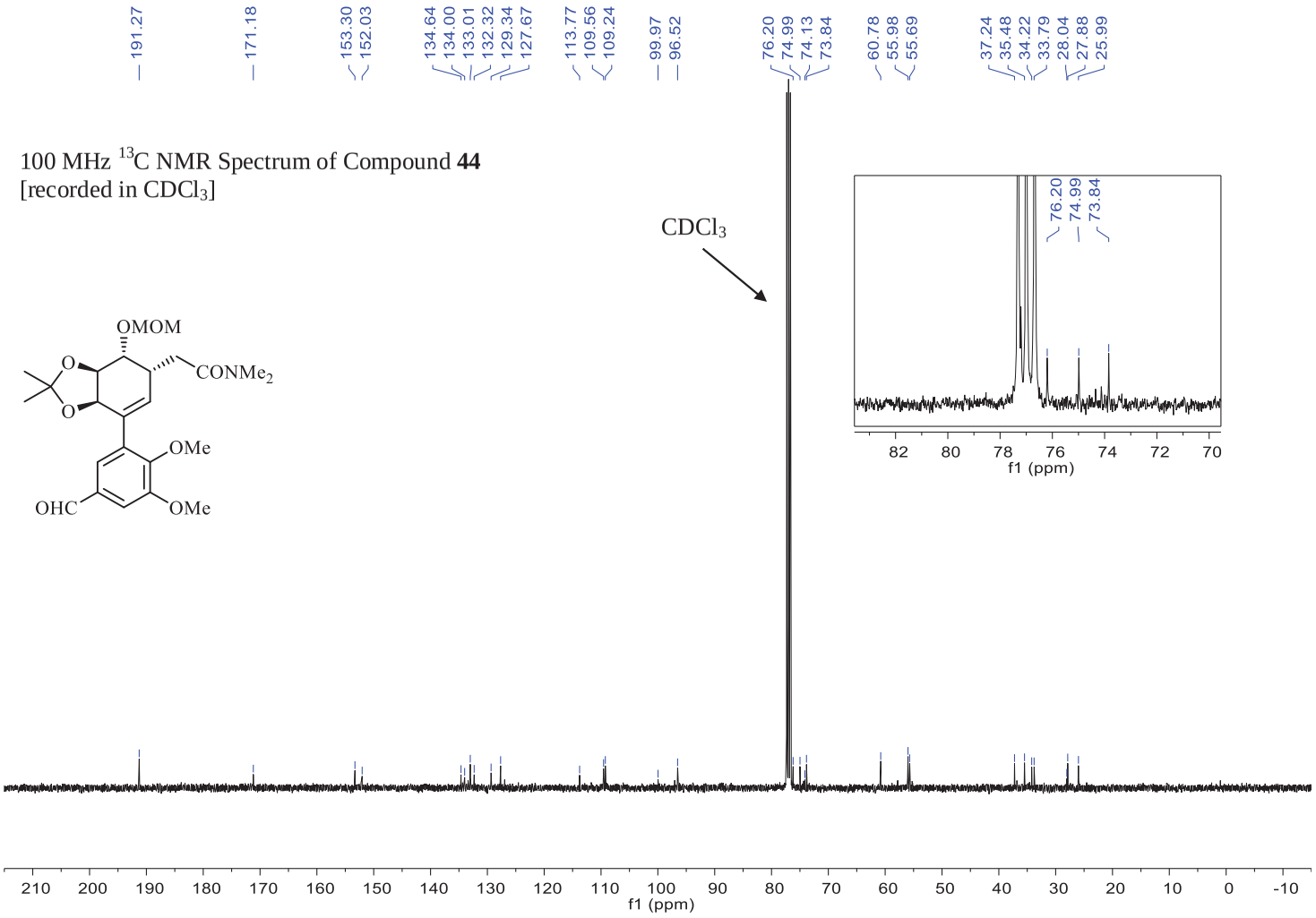
100 MHz ^{13}C NMR Spectrum of Compound **43**
[recorded in $CDCl_3$]



400 MHz ^{1}H NMR Spectrum of Compound **44**
[recorded in $CDCl_3$] * = minor regioisomer



100 MHz ^{13}C NMR Spectrum of Compound **44**
[recorded in $CDCl_3$]



Publication Four

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THE SYNTHESIS OF POLYFUNCTIONALIZED, CYCLOHEXENE-BASED CHIRONS FROM TARTARIC ACID†

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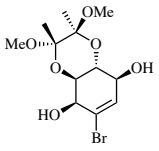
† Dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday and in recognition of his sustained and outstanding contributions to chemical synthesis

Abstract – Compound *ent*-**1** as well as certain related homochiral and polyfunctionalized cyclohexenes have been prepared from the 1,2-diacetal **4** that is itself readily derived from *L*-tartaric acid (**3**). Grignard addition and ring-closing metathesis processes constitute the key steps associated with the reaction sequences involved. This work provides a method for obtaining a range of potentially useful cyclohexenone-containing chirons that are enantiomerically related to those that have been prepared from the homochiral *cis*-1,2-dihydrocatechol **2**, the product of the microbial biotransformation of bromobenzene.

INTRODUCTION

In connection with a study focused on acetylcholine esterase (AChE) inhibitors, we prepared, over five steps, the polyfunctionalized and homochiral α-bromocyclohexenone **1** from the enantiomerically pure *cis*-1,2-dihydrocatechol **2**.[1] Compound **2** is the product of the microbial dihydroxylation of bromobenzene, a transformation that can be achieved particularly effectively with a genetically-engineered strain of *E. coli* that over-expresses the enzyme toluene dioxygenase (TDO).[2] In order to fully explore the biological profiles of the AChE inhibitors in question, we required the enantiomer of compound **1**, namely *ent*-**1**. While a logical precursor to this brominated cyclohexene is the *cis*-1,2-dihydrocatechol *ent*-**2**, the latter is not as readily accessible, especially in homochiral form, as congener **2**.[3] Accordingly, we sought another means for obtaining chiron *ent*-**1** as well as related systems that could serve as valuable building blocks for the synthesis of various polyoxygenated cyclohexenes and their saturated counterparts.



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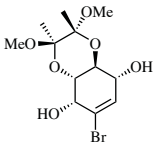

ent-**1**

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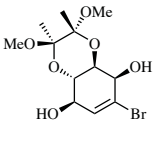


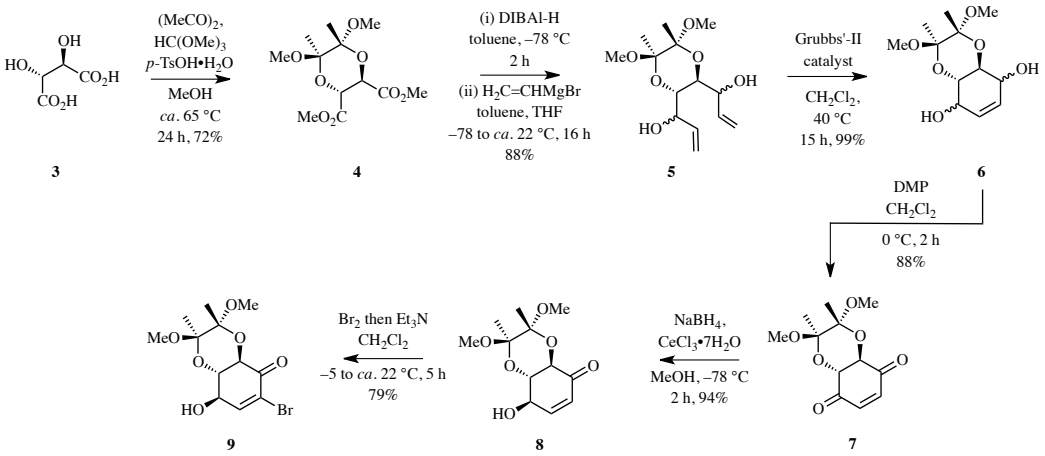
ent-**1**

ent-**2**

The groups of Madsen,[4] Sulikowski[5] and Yan[6] have each demonstrated that the acetonide derived from *D*- or *L*-tartaric acid can be elaborated, *via* manipulation of the derived ester residues using reduction, vinyl Grignard addition and then ring-closing metathesis (RCM) steps, into various conduritols or amino pseudosugars. Prasad has described[7] closely related chemistries. The RCM products so formed incorporate rather unstable acetonide-protected cyclohex-4-ene-*trans*-1,2-diol moieties. On the other hand, and during the course of establishing a total synthesis the macrolide antascomicin B (a potential immunosuppressive agent), Ley[8] and co-workers used a butanediacetal-protected dimethyl tartrate to construct, *via* a late-stage RCM, a complex cyclohexene annulated to a 1,4-dioxane and that embodies a stable masked *trans*-1,2-diol moiety. Herein we report on the exploitation of these types of protocols in the synthesis of the target chiron *ent*-**1** as well as a range of analogues that are likely to be of value in the synthesis of a variety of biologically active systems.

RESULTS AND DISCUSSION

The preparation of a series of poly-oxygenated and homochiral cyclohexenes from *L*-tartaric acid (**3**) is shown in Scheme 1 and started with the formation, under standard and operationally simple conditions, of diacetal diester **4** (72%). Reduction of the latter compound to the corresponding dialdehyde was achieved using di-*iso*-butylaluminium hydride (DIBAl-H) in toluene at –78 °C and this was immediately reacted with vinylmagnesium bromide[5] to give the bis-olefin **5** as an inseparable mixture of diastereoisomers in 88% combined yield. This mixture was treated with the Grubbs'-II catalyst in dichloromethane and so effecting a RCM reaction and thus forming a *ca*. 10:6:3 mixture of the three possible stereoisomeric forms of the anticipated cyclohexene **6** in 99% combined yield.



Scheme 1

This mixture of cyclohexenes, which was characterized as such, was subjected to a two-fold oxidation with the Dess-Martin periodinane (DMP) and so affording the corresponding enedione **7** in 88% yield.

While enedione **7** was prone to two-fold enolization and concomitant formation of the isomeric hydroquinone,[9] this C_2-symmetric compound could be stereoselectively reduced to the γ-hydroxyenone **8** (94%) under Luche-type conditions. Confirmation of the stereochemical outcome associated with this conversion, which involves axial delivery of hydride,[10] was achieved through the single-crystal X-ray analysis of a halogenated derivative. Specifically, successive treatment of compound **8** with molecular

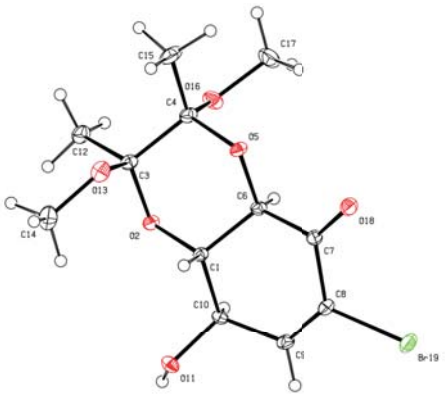
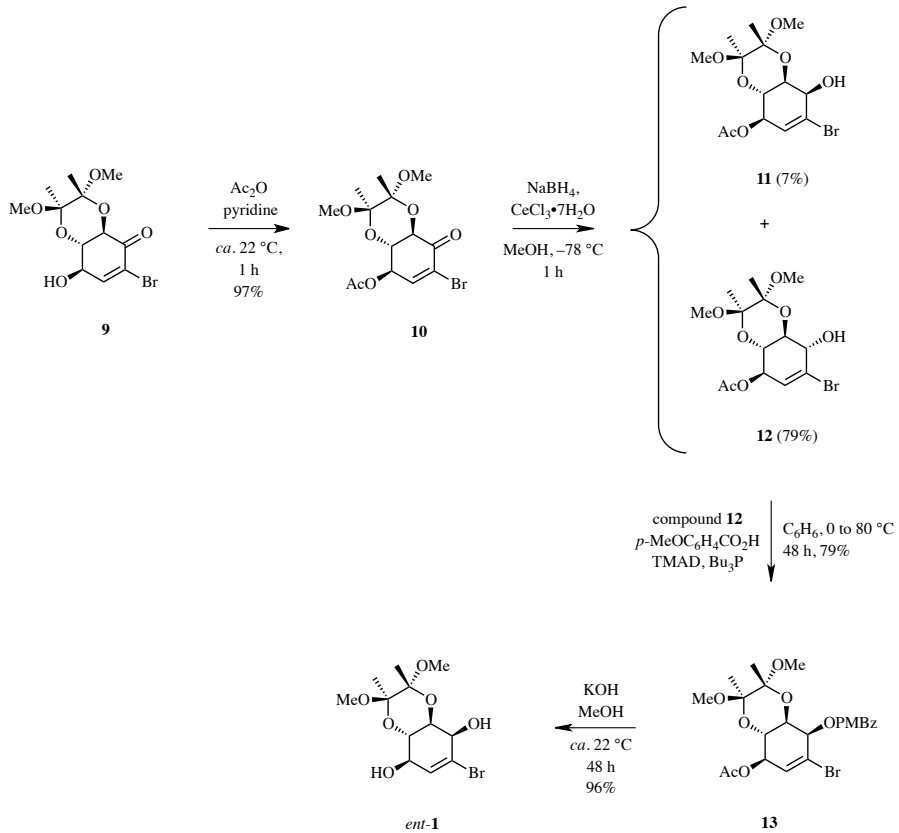


Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **9** (CCDC No. 1491822). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

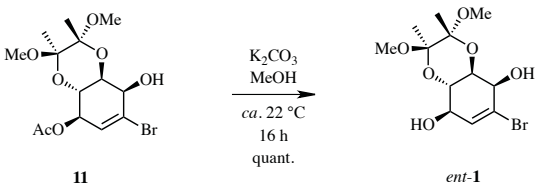
bromine then triethylamine at 0 °C[11] afforded the crystalline α-bromoenone **9** (79% yield) that was subjected to such an analysis. The derived ORTEP is shown in Figure 1 while other results of this analysis are provided in the Experimental Section.

The completion of the synthesis of the target synthon *ent*-**1** followed the pathway shown in Scheme 2 and involved the conversion of the γ-hydroxyenone **9** into the corresponding acetate, **10** (97%), under standard conditions. Luche reduction of compound **10** afforded a diastereoisomeric and chromatographically separable mixture of compounds **11** (7%) and **12** (79%). Subjection of the latter product to a Mitsunobu reaction, using *p*-methoxybenzoic acid as nucleophile and the *N*,*N*,*N*',*N*'-tetramethylazodicarboxamide (TMAD)/tri-*n*-butylphosphine reagent combination,[12] then afforded ester **13** (79%). Finally, cleavage of this ester using potassium hydroxide in methanol gave the target *ent*-**1** in 96% yield.



Scheme 2

The minor product, **11**, derived from the reduction of α-bromoenone **10** was readily and nearly quantitatively converted into compound *ent*-**1** through treatment (Scheme 3) with potassium carbonate in methanol. All the spectral data acquired on compound *ent*-**1** were consistent with the assigned structure and matched those recorded[1] on its enantiomer (*viz*. **1**) save for the specific rotation that was of similar magnitude but opposite in sign {*viz*. –76.5 (*c* 1.0 in $CHCl_3$) for *ent*-**1** *vs* +72.6 (*c* 1.1 in $CHCl_3$) for **1**}. Given this relationship and that the structure of compound **1** has been established through the single-crystal X-ray analysis of a derivative,[1] the illustrated stereochemical array within compound *ent*-**1** is secure.



11 *ent*-**1**

Scheme 3

Considering the ready availability of both *D*- and *L*-tartaric acid and the demonstrated utility of polyoxygenated and halogenated cyclohexenes in the synthesis,[2] the simple protocols defined above should provide a useful new means for the assembly of biologically active systems, especially various conduritols and related compounds.[15] Work directed towards such ends is now underway in our laboratories. Results will be reported in due course.

EXPERIMENTAL

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are presented as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.1(6) were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer UTAR Two FTIR Spectrometer. Samples were analyzed as either thin films or finely divided solids. Low-resolution ESI mass spectra were recorded on a Micromass LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while high-resolution measurements were conducted on an LCT Premier time-of-flight

instrument. Low- and high-resolution EI mass spectra were recorded on an Autospec Premier Micromass magnetic-sector machine. Optical rotations were recorded in $CHCl_3$ at 20 °C on a Perkin Elmer Model 343 Polarimeter. Melting points were measured on an Optimelt™ automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*[13] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Diethyl ether, *N*,*N*-dimethylformamide (DMF), CH_2Cl_2 and EtOAc were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[14] Where necessary, reactions were performed under an inert atmosphere.

Specific Experimental Procedures and Product Characterization

Dimethyl (2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate (4)

Using a modification of a procedure reported[16] by Maycock and co-workers, a magnetically stirred solution of *L*–tartaric acid (11.87 g, 79.09 mmol), 2,3-butanedione (7.25 mL, 80 mmol) and trimethyl orthoformate (50 mL, 466 mmol) in dry MeOH (100 mL) was treated with *p*-toluenesulfonic acid monohydrate (710 mg, 5 mol%). The resulting solution was heated under reflux for 24 h and the ensuing deep-red mixture then cooled to room temperature and neutralized with $NaHCO_3$ (4.00 g). Stirring was continued for 0.5 h then the reaction mixture was concentrated under reduced pressure. The residue thus obtained was diluted with EtOAc (100 mL) then $NaHCO_3$ (30 mL of a saturated aqueous solution) added and the separated organic phase washed with $NaHCO_3$ (1 × 30 mL of a saturated aqueous solution) then water (1 × 30 mL). The combined aqueous layers were extracted with EtOAc (3 × 30 mL) and the combined organic phases then washed with brine (2 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow solid thus obtained was recrystallized (hexane/EtOAc) and the resulting solid collected and washed successively with ice-cold hexane and ice-cold EtOAc to give bis-ester **4**[16,17] (16.73 g, 72%) as an off-white, crystalline solid, mp 107–108 ºC (lit.[17] mp 106–108 °C), $[\alpha]_D$ –135.7 (*c* 1.1, $CHCl_3$) {lit.[17] $[\alpha]_D$ –139.6 (*c* 1.0, $CHCl_3$)} [Found: $(M + K)^+$, 331.0777. $C_{12}H_{20}KO_8$ requires $(M + K)^+$, 331.0795]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 4.54 (s, 2H), 3.77 (s, 6H), 3.32

(s, 6H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 168.6, 99.4, 68.9, 52.7, 48.6, 17.5; IR (solid) ν_{max} 2992, 1736, 1443, 1377, 1282, 1202, 1139, 1110, 1026, 898, 886, 810, 744 cm^{-1}; MS (ESI, +ve) *m/z* 315 [(M + Na)$^+$, 100%].

1,1'-((2*S*,3*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(prop-2-en-1-ol) (5)

A magnetically stirred solution of bis-ester **4** (3.10 g, 10.63 mmol) in dry toluene (30 mL) was cooled to –78 ºC then DIBAl-H (22.3 mL of a 1 M solution in toluene, 22.3 mmol) added, *via* syringe-pump, over 0.75 h. The ensuing mixture was stirred at –78 ºC for 2 h then vinylmagnesium bromide (74.4 mL of a 1 M solution in THF, 74.4 mmol) was added dropwise over 0.5 h. The solution thus formed was stirred at –78 ºC for 0.5 h then allowed to warm to room temperature. After 16 h the reaction mixture was cooled to 0 ºC, quenched with Rochelle salt (100 mL of a saturated solution: CAUTION slow addition required) then re-warmed to room temperature and stirring continued for 3 h. The resulting biphasic mixture was transferred to a separating funnel and the organic layer separated then washed with water (1 × 100 mL). The combined aqueous layers were extracted with EtOAc (3 × 30 mL) and the combined organic phases then washed with brine (3 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing thick, orange oil was subjected to flash column chromatography (silica, hexane → 1:1 v/v EtOAc/hexane gradient elution) and concentration of appropriate fractions (R_f = 0.5 in 1:1 v/v EtOAc/hexane) afforded bis-allylic alcohol **5** (2.69 g, 88%) as a clear, colorless oil and a mixture of diastereoisomers [Found: (M + Na)$^+$, 311.1465. $C_{14}H_{24}NaO_6$ requires (M + Na)$^+$, 311.1471]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (mixture of three diastereoisomers) 6.12–5.94 (complex m, 2H), 5.40–5.15 (series of m, 4H), 4.31–4.17 (complex m, 2H), 4.03–3.65 (series of m, 2H), 3.24–3.19 (4 × s, 6H), 2.70–2.30 (series of m, 2H), 1.28–1.27 (3 × s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C (mixture of three diastereoisomers) 138.1, 138.0, 136.7(2), 136.6(8), 117.2, 116.8, 116.1, 115.8, 99.0, 98.9, 98.8(1), 98.7(9), 72.6, 72.3, 72.1, 71.6, 71.3, 70.5, 48.1(0), 48.0(6), 17.6(1), 17.5(9), 17.5; IR (film) ν_{max} 3407, 2991, 2949, 2833, 1375, 1121, 1036, 997, 921, 852 cm^{-1}; MS (ESI, +ve) *m/z* 311 [(M + Na)$^+$, 100%].

(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxine-5,8-diol (6)

A solution of the bis-allylic alcohol **5** (2.67 g, 9.25 mmol) in CH_2Cl_2 (200 mL) was sonicated under an atmosphere of nitrogen for 0.5 h then Grubbs'-II catalyst (157 mg, 2 mol%) was added in one portion. The ensuing mixture was heated under reflux for 1.5 h then cooled to room temperature and the solvent removed under reduced pressure. The resulting brown solid was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/hexane → EtOAc gradient elution) and concentration of appropriate fractions (R_f = 0.3 in 2:1 v/v EtOAc/hexane) afforded cyclohexene **6** (2.39 g, 99%) as a white, amorphous solid and a mixture of diastereoisomers [Found: (M + Na)$^+$, 283.1165. $C_{12}H_{20}NaO_6$ requires (M + Na)$^+$, 283.1158]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H (mixture of three diastereoisomers) 6.07–5.62

(series of m, 2H), 4.51–4.20 (complex m, 2H), 4.10–3.57 (series of m, 2H), 3.49 (broad m, 1H), 3.36–3.24 (4 × s, 6H), 2.64–2.09 (series of broad m, 1H), 1.39–1.28 (4 × s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 132.9, 130.0, 129.3, 126.6, 100.0, 99.8, 99.3, 99.1, 72.5, 70.6, 70.3, 69.7, 67.9, 65.9, 65.5, 65.3, 48.3, 48.2, 48.1(3), 48.0(7), 17.9(4), 17.9(0), 17.8(2), 17.8(0); IR (solid) ν_{max} 3313, 2948, 1465, 1373, 1204, 1117, 1030, 971, 915, 886, 847 cm^{-1}; MS (ESI, +ve) *m/z* 283 [(M + Na)$^+$, 100%].

(2*R*,3*R*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydrobenzo[*b*][1,4]dioxine-5,8-dione (7)

Dess-Martin periodane (23.80 g, 53.31 mmol) was added, in portions, to a magnetically stirred solution of compound **6** (4.63 g, 17.78 mmol) in CH_2Cl_2 (25 mL) maintained at 0 ºC. After addition was complete (0.25 h) the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h before being concentrated under reduced pressure at 20 ºC. The residue thus obtained was subjected to rapid flash chromatography (silica, 2:8 v/v pentane/Et_2O elution) and concentration of the relevant fractions (R_f = 0.7 in 1:2 v/v CH_2Cl_2/Et_2O) at 20 ºC afforded enedione **7** (4.01 g, 88%) as a bright yellow, crystalline solid, mp 115–117 ºC (dec.), $[\alpha]_D$ –121.0 (*c* 0.9 in $CHCl_3$) [Found: (M + Na)$^+$, 279.0850. $C_{12}H_{16}NaO_6$ requires (M + Na)$^+$, 279.0845]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.84 (s, 2H), 4.73 (s, 2H), 3.26 (s, 6H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 192.1, 140.1, 100.6, 73.9, 48.7, 17.6; IR (solid) ν_{max} 2954, 2849, 1699, 1380, 1133, 1113, 1027, 823, 543 cm^{-1}; MS (ESI, +ve) *m/z* 343 [(M + 2 × CH_3OH + Na)$^+$, 100%], 311 [(M + CH_3OH + Na)$^+$, 50], 279 [(M + Na)$^+$, 10].

(2*R*,3*R*,4a*R*,8*R*,8a*S*)-8-Hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,8,8a-tetrahydrobenzo[*b*][1,4]dioxin-5(4a*H*)-one (8)

Sodium borohydride (770 mg, 20.35 mmol) was added, in portions over 0.08 h, to a magnetically stirred solution of $CeCl_3$•$7H_2O$ (7.60 g, 20.40 mmol) in MeOH (50 mL) maintained at 0 ºC. The ensuing mixture was stirred at this temperature for 0.25 h then transferred to a pressure-equalized dropping funnel and added dropwise to a magnetically solution of endione **7** (4.01 g, 15.67 mmol) in MeOH (150 mL) that had been cooled to –78 ºC. After 1.5 h further portions of $NaBH_4$ (5 × 10 mg, 1.32 mmol) were slowly added until the yellow reaction mixture became colorless and at which point it was quenched with acetone (20 mL). NH_4Cl (100 mL of a saturated aqueous solution) was added to the reaction mixture so-formed that was then allowed to warm to room temperature. The ensuing mixture was concentrated under reduced pressure and the residue thus obtained diluted with EtOAc (100 mL) and water (50 mL). The separated aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic phases then washed with brine (2 × 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus generated was subjected to flash column chromatography (silica, CH_2Cl_2 → 1:2 v/v Et_2O/CH_2Cl_2 gradient elution) and concentration of appropriate fractions (R_f = 0.2 in 1:1 v/v EtOAc/hexane) afforded enone **8** (3.79 g, 94%) as a clear, colorless oil, $[\alpha]_D$ –215.0 (*c* 0.5, $CHCl_3$)

[Found: $(M + Na)^+$, 281.1006. $C_{12}H_{18}NaO_6$ requires $(M + Na)^+$, 281.1001]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.85 (dd, J = 10.5 and 2.0 Hz, 1H), 6.07 (dd, J = 10.5 and 2.6 Hz, 1H), 4.67 (m, 1H), 4.25 (d, J = 11.4 Hz, 1H), 3.96 (dd, J = 11.4 and 8.7 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.55 (d, J = 3.9 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 193.5, 148.6, 128.4, 100.3, 99.4, 74.3, 72.3, 70.1, 48.7, 48.2, 17.7(3), 17.6(6); IR (film) ν_{max} 3452, 2958, 1683, 1379, 1118, 1028, 967, 947, 881, 806, 634, 585, 540 cm^{-1}; MS (ESI, +ve) *m/z* 281 [$(M + Na)^+$, 100%].

(2*R*,3*R*,4a*R*,8*R*,8a*S*)-6-Bromo-8-hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,8,8a-tetrahydrobenzo[*b*][1,4]dioxin-5(4a*H*)-one (9)

Molecular bromine (400 μL of a 10% v/v solution in CH_2Cl_2, 0.79 mmol) was added, dropwise, to a magnetically stirred solution of enone **8** (185 mg, 0.72 mmol) in CH_2Cl_2 maintained at –5 ºC. The resulting solution was stirred at this temperature for 1 h then triethylamine (300 μL, 2.15 mmol) added dropwise. The cooling bath was then removed and the reaction mixture stirred at room temperature for 16 h before being quenched with sodium sulfite (2 mL of a saturated aqueous solution). The separated organic layer was washed successively with sodium sulfite (3 × 5 mL of a saturated aqueous solution) and NH_4Cl (3 × 5 mL of an aqueous solution) then the combined aqueous washings were extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (2 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, CH_2Cl_2 → 1:9 v/v Et_2O/CH_2Cl_2 gradient elution) and concentration of appropriate fractions (R_f = 0.2 in 1:9 v/v Et_2O/CH_2Cl_2) afforded bromoenone **9** (190 mg, 79 %) as a white, crystalline solid, mp 178–181 °C, $[\alpha]_D$ –146.6 (*c* 0.5, $CHCl_3$) [Found: $(M + Na)^+$, 359.0100. $C_{12}H_{17}{}^{79}BrNaO_6$ requires $(M + Na)^+$, 359.0106]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.29 (d, J = 2.3 Hz, 1H), 4.63 (ddd, J = 8.6, 4.1 and 2.3 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 3.98 (dd, J = 11.4 and 8.6 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.57 (d, J = 4.1 Hz, 1H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 186.3, 148.6, 123.2, 100.5, 99.3, 73.6, 71.6, 70.5, 48.8, 48.3, 17.6(3), 17.5(9); IR (solid) ν_{max} 3480, 2945, 1712, 1601, 1450, 1373, 1334, 1279, 1205, 1141, 1110, 1023, 907, 888, 870, 858, 606, 782, 663, 606, 517, 440 cm^{-1}; MS (ESI, +ve) *m/z* 361 and 359 [$(M + Na)^+$, 98 and 100%, respectively].

(2*R*,3*R*,4a*S*,5*R*,8a*R*)-7-Bromo-2,3-dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl acetate (10)

Acetic anhydride (120 μL, 1.25 mmol) was added to a magnetically stirred solution of bromoenone **9** (140 mg, 0.416 mmol) in pyridine (5 mL). Stirring was continued at room temperature for 1 h then the reaction mixture was concentrated under reduced pressure to afford acetate **10** (153 mg, 97%) as a white foam, $[\alpha]_D$ –366.5 (*c* 0.6, $CHCl_3$) [Found: $(M + Na)^+$, 401.0217. $C_{14}H_{19}{}^{79}BrNaO_7$ requires $(M + Na)^+$, 401.0212]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.13 (d, J = 2.4 Hz, 1H), 5.67 (dd, J = 8.9 and 2.4 Hz, 1H),

4.39 (d, *J* = 11.2 Hz, 1H), 4.18 (dd, *J* = 11.2 and 8.9 Hz, 1H), 3.29 (s, 3H), 3.25 (s, 3H), 2.16 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 185.9, 170.1, 144.8, 124.3, 100.5, 99.3, 71.7, 71.0, 70.6, 48.7, 48.1, 20.9, 17.6, 17.5; IR (solid) ν_{max} 2952, 1751, 1720, 1377, 1220, 1135, 1113, 1028, 979, 918, 886, 853, 786, 662 cm^{-1}; MS (ESI, +ve) *m/z* 467 and 465 [(M + 2 × CH_3OH + Na), 98 and 100%, respectively], 403 and 401 [$(M + Na)^+$, 30 and 29, respectively].

(2*R*,3*R*,4a*S*,5*R*,8a*R*)-7-Bromo-2,3-dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl acetate (11) and (2*R*,3*R*,4a*S*,5*R*,8*S*,8a*S*)-7-Bromo-8-hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl acetate (12)

Sodium borohydride (211 mg, 5.59 mmol) was added, in portions over 0.08 h, to a magnetically stirred solution of $CeCl_3$•$7H_2O$ (1.09 g, 2.93 mmol) in MeOH (20 mL) maintained at 0 ºC. The ensuing mixture was stirred at this temperature for 0.25 h then transferred to a pressure-equalized dropping funnel and added dropwise to a magnetically solution of acetate **10** (1.06 g, 2.79 mmol) in MeOH (100 mL) maintained at –78 ºC. After 1 h the reaction mixture was allowed to warm to room temperature, quenched with water (5 mL) and concentrated under reduced pressure. The residue thus obtained was diluted with EtOAc (100 mL) and NH_4Cl (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic phases then washed with brine (2 × 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v Et_2O/CH_2Cl_2) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:19 v/v Et_2O/CH_2Cl_2) afforded compound **11** (76 mg, 7%) as a clear, colorless oil, $[\alpha]_D$ –160.0 (*c* 0.9, $CHCl_3$) [Found: $(M + Na)^+$, 403.0373. $C_{14}H_{21}{}^{79}BrNaO_7$ requires $(M + Na)^+$, 403.0368]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.12 (d, *J* = 2.5 Hz, 1H), 5.30 (dd, *J* = 8.4 and 2.5 Hz, 1H), 4.35 (d, *J* = 4.0 Hz, 1H), 4.16 (dd, *J* = 11.0 and 8.4 Hz, 1H), 3.78 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.27 (s, 3H), 3.26 (s, 3H), 2.74 (broad s, 1H), 2.09 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 170.5, 130.6, 123.8, 100.1, 99.3, 72.2, 72.1, 67.6, 65.1, 48.4, 48.0, 21.1, 17.8, 17.7; IR (film) ν_{max} 3475, 2950, 1750, 1733, 1371, 1230, 1135, 1116, 1033, 970, 933, 886, 851, 732 cm^{-1}; MS (ESI, +ve) *m/z* 405 and 403 [$(M + Na)^+$, 100 and 98%, respectively].

Concentration of fraction B (R_f = 0.2 in 1:19 v/v Et_2O/CH_2Cl_2) afforded compound **12** (840 mg, 79%) as a clear, colorless oil, $[\alpha]_D$ –204.7 (*c* 0.9, $CHCl_3$) [Found: $(M + Na)^+$, 403.0367. $C_{14}H_{21}{}^{79}BrNaO_7$ requires $(M + Na)^+$, 403.0368]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.04 (app. t, *J* = 2.1 Hz, 1H), 5.38 (m, 1H), 4.35 (m, 1H), 3.90 (dd, *J* = 11.0 and 8.3 Hz, 1H), 3.81 (dd, *J* = 11.0 and 7.8 Hz, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 2.53 (s, 1H), 2.09 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 170.3, 128.5, 127.1, 99.4, 99.2, 72.1, 71.8, 71.4, 68.6, 48.2, 48.0, 21.1, 17.7, 17.6; IR (film) ν_{max} 3474, 2919, 2850, 1737, 1369, 1229, 1118, 1020, 969, 914, 886, 852, 795, 736 cm^{-1}; MS (ESI, +ve) *m/z* 405 and 403 [$(M + Na)^+$,

100 and 98%, respectively].

(2*R*,3*R*,4a*R*,5*R*,8*R*,8a*S*)-8-Acetoxy-6-bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydro-benzo[*b*][1,4]dioxin-5-yl 4-methoxybenzoate (13)

Tri-*n*-butylphosphine (520 μL, 2.08 mmol) was added to a magnetically stirred solution of allylic alcohol **12** (397 mg, 1.04 mmol) and *p*-methoxybenzoic acid (316 mg, 2.08 mmol) in benzene (7 mL). The solution thus obtained was cooled to 0 ºC then *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) (376 mg, 2.08 mmol) was added in one portion. The ensuing mixture was stirred at 0 °C for 0.25 h then heated under reflux for 48 h. The cooled solution was filtered through a short pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, CH_2Cl_2 → 1:19 v/v Et_2O/CH_2Cl_2 gradient elution) and concentration of appropriate fractions (R_f = 0.5 in 1:9 v/v Et_2O/CH_2Cl_2) afforded ester **13** (422 mg, 79%) as a white, amorphous solid, $[\alpha]_D$ –28.3 (*c* 1.1, $CHCl_3$) [Found: $(M + Na)^+$, 537.0734. $C_{22}H_{27}{}^{79}BrNaO_9$ requires $(M + Na)^+$, 537.0736]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.05 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.24 (d, *J* = 2.5 Hz, 1H), 5.97 (d, *J* = 4.2 Hz, 1H), 5.37 (dd, *J* = 8.5 and 2.5 Hz, 1H), 4.28 (dd, *J* = 11.1 and 8.5 Hz, 1H), 3.95 (dd, *J* = 11.1 and 4.2 Hz, 1H), 3.88 (s, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 2.14 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 170.4, 165.8, 163.6, 132.6, 132.3, 122.5, 121.0, 113.7, 99.6, 99.3, 72.2, 71.9, 66.7, 66.0, 55.6, 48.4, 47.9, 21.1, 17.7, 17.4; IR (film) ν_{max} 2980, 1724, 1605, 1511, 1372, 1254, 1226, 1166, 1117, 1083, 1051, 1028, 971, 933, 765, 699, 663, 611 cm^{-1}; MS (ESI, +ve) *m/z* 539 and 537 [$(M + Na)^+$, 100 and 98%, respectively].

(2*R*,3*R*,4a*S*,5*R*,8*R*,8a*S*)-6-Bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]-dioxine-5,8-diol (*ent*-1)

*Method i (ex. Compound **13**)*: Potassium hydroxide (60 mg, 1.07 mmol) was added to a magnetically stirred solution of compound **13** (103 mg, 0.20 mmol) in MeOH (10 mL) and the ensuing mixture stirred at room temperature for 48 h. The MeOH was then removed under reduced pressure and the residue thus obtained diluted with EtOAc (10 mL) and NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic phases washed with brine (2 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting white solid was subjected to flash column chromatography (silica, → 1:24 v/v Et_2O/CH_2Cl_2 gradient elution) and concentration of appropriate fractions (R_f = 0.3 in 1:19 v/v $MeOH/CH_2Cl_2$) afforded enediol *ent*-**1** (65 mg, 96%) as a white foam, $[\alpha]_D$ –76.5 (*c* 1.0, $CHCl_3$) [Found: $(M + Na)^+$, 361.0260. $C_{12}H_{19}{}^{79}BrNaO_6$ requires $(M + Na)^+$, 361.0263]. ^{1}H NMR (CD_3OD, 400 MHz) δ_H 6.05 (d, *J* = 2.5 Hz, 1H), 4.22 (d, *J* = 4.1 Hz, 1H), 4.06 (dd, *J* = 7.9 and 2.5 Hz, 1H), 3.87 (dd, *J* = 11.1 and 7.9 Hz, 1H), 3.63 (dd, *J* = 11.1 and 4.1 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (CD_3OD, 100 MHz) δ_C 135.3, 124.0, 100.8, 100.2, 73.1,

71.8, 69.9, 69.2, 48.3(1), 48.2(5), 18.1, 18.0; IR (film) ν_{max} 3236, 3007, 2954, 2905, 2834, 1114, 1074, 1054, 1030, 985, 912, 884, 852, 760, 665, 617, 599 cm^{-1}; MS (ESI, +ve) *m/z* 363 and 361 [$(M + Na)^+$, 98 and 100%, respectively].

*Method ii (ex. Compound **11**)*: Potassium carbonate (50 mg, 0.36 mmol) was added to a magnetically stirred solution of ester **11** (76 mg, 0.20 mmol) in MeOH (10 mL) and the resulting mixture stirred at room temperature for 12 h then concentrated under reduced pressure. The residue thus obtained was diluted with EtOAc (10 mL) and water (10 mL) then the separated aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (2 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give enediol *ent*-**1** (67 mg, 99%) as a white foam. This material was identical, in all respects, with that obtained by Method i.

X-Ray Crystallographic Study

Crystallographic Data

Compound 9: $C_{12}H_{17}BrO_6$, M = 337.17, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.8265(1), b = 11.4217(1), c = 17.8288(1) Å; V = 1390.12(1) $Å^3$; D_x = 1.611 g cm^{-3}; 2750 unique data ($2\theta_{max}$ 144.6°), R = 0.021 [for 2718 reflections with $I > 2.0\sigma(I)$]; Rw = 0.052 (all data), S = 1.03.

Structure Determination

Images were measured on an Agilent SuperNova CCD diffractometer (CuKα, mirror monochromator, λ = 1.54184 Å) and data extracted using the CrysAlis package.[18] Structure solution was by direct methods (SIR92).[19] The structure of compound **9** was refined using the CRYSTALS program package.[20] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1491822). These data can be obtained free-of-charge *via* www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Supplementary Material

The ^1H and ^{13}C NMR spectra of compounds **4**–**13** and *ent*-**1** are available on the Journal's website.

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SUPPORTING INFORMATION FOR:

The Synthesis of Polyfunctionalized, Cyclohexene-based Chirons from Tartaric Acid

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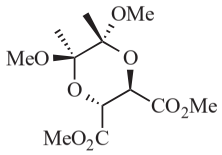

400 MHz ^{1}H NMR Spectrum of Compound **4**
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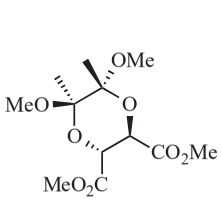

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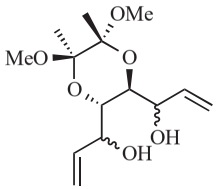

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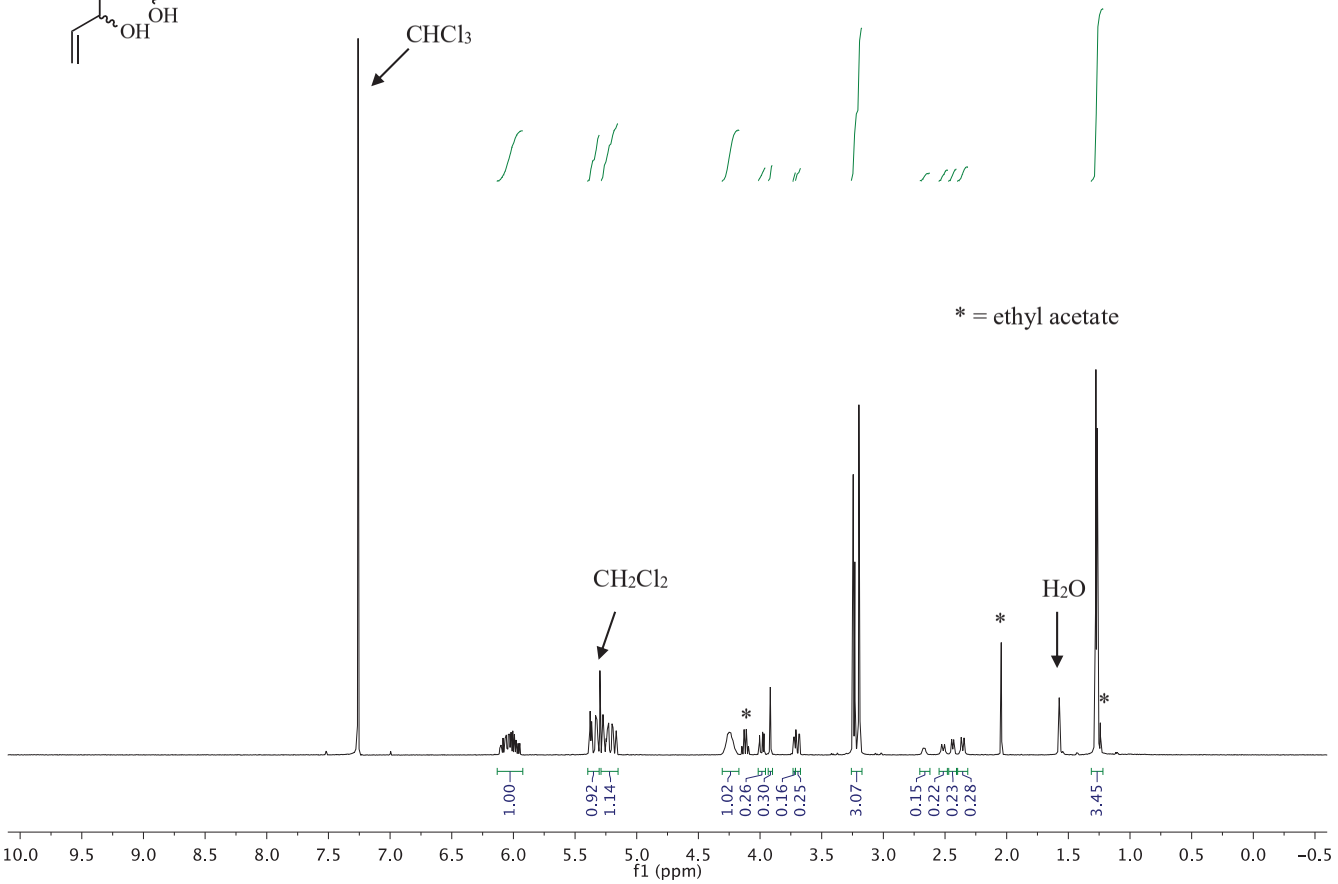

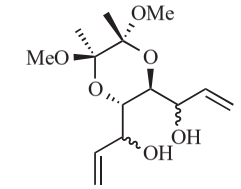

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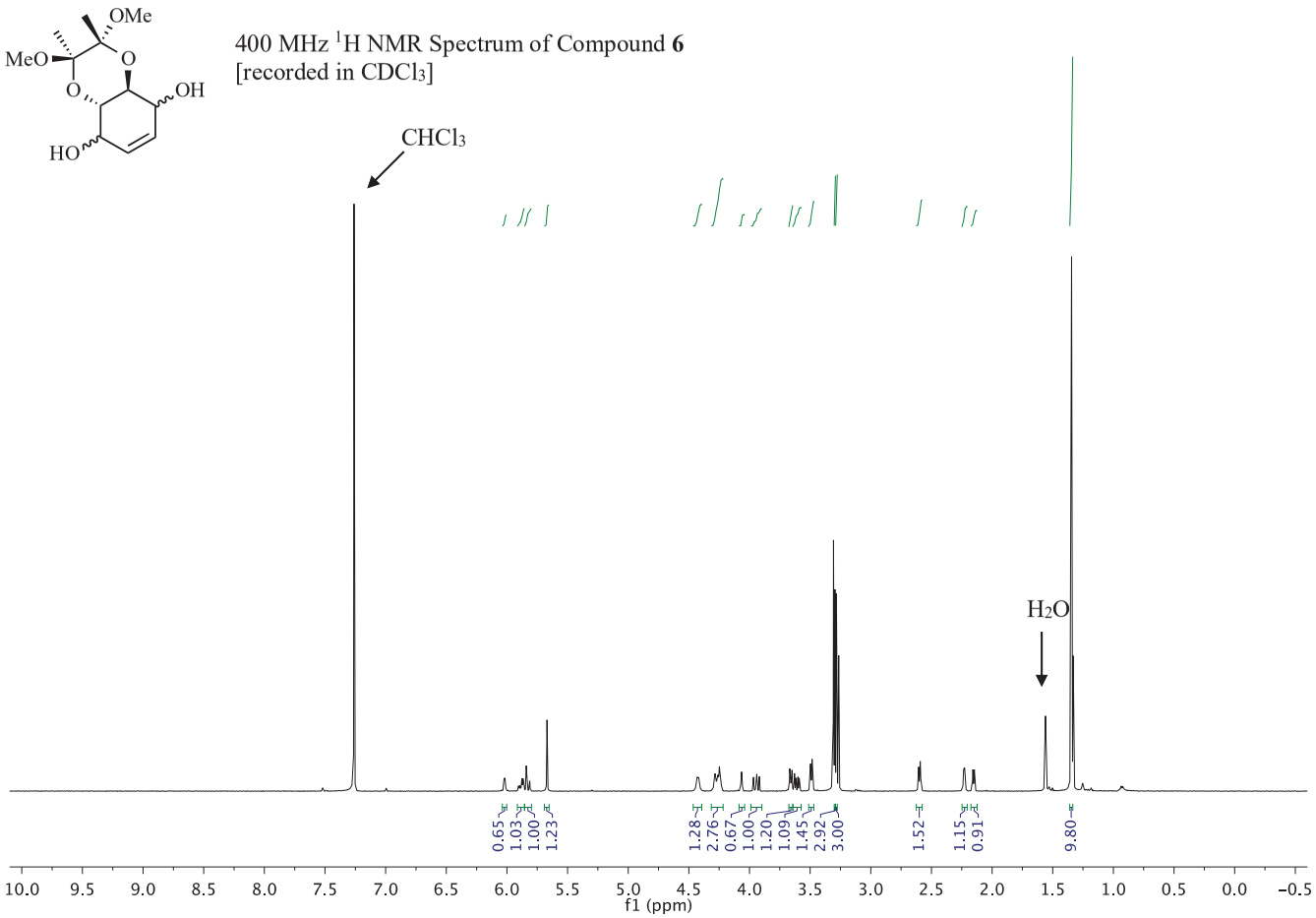
OMe
MeO
O
O
OH
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400 MHz ^{1}H NMR Spectrum of Compound **6**
[recorded in $CDCl_3$]
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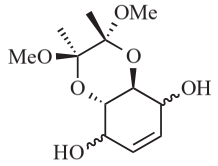
1.03
1.00
1.23
1.28
2.76
0.67
1.00
1.20
1.09
1.45
2.92
3.00
1.52
1.15
0.91
9.80
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



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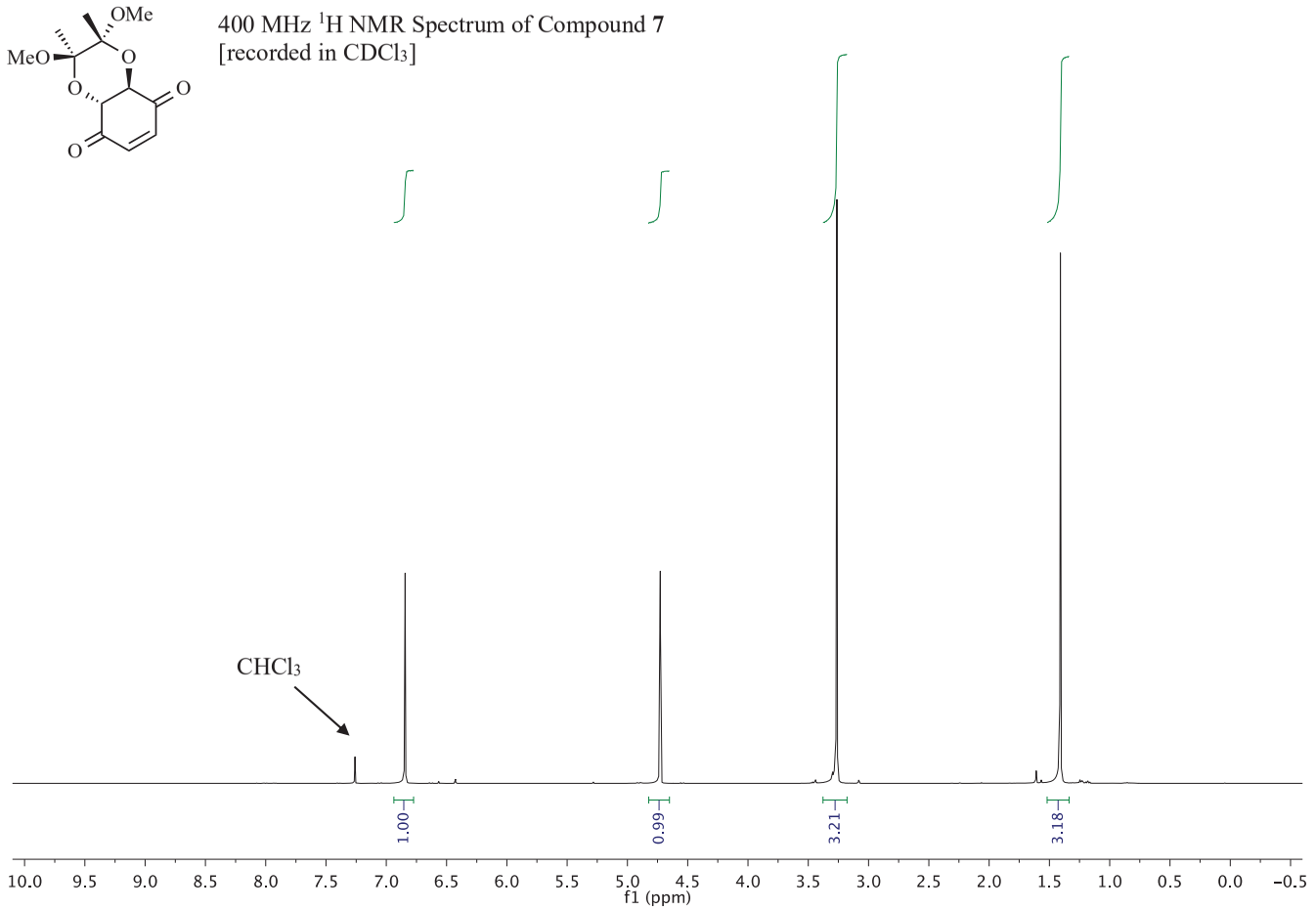
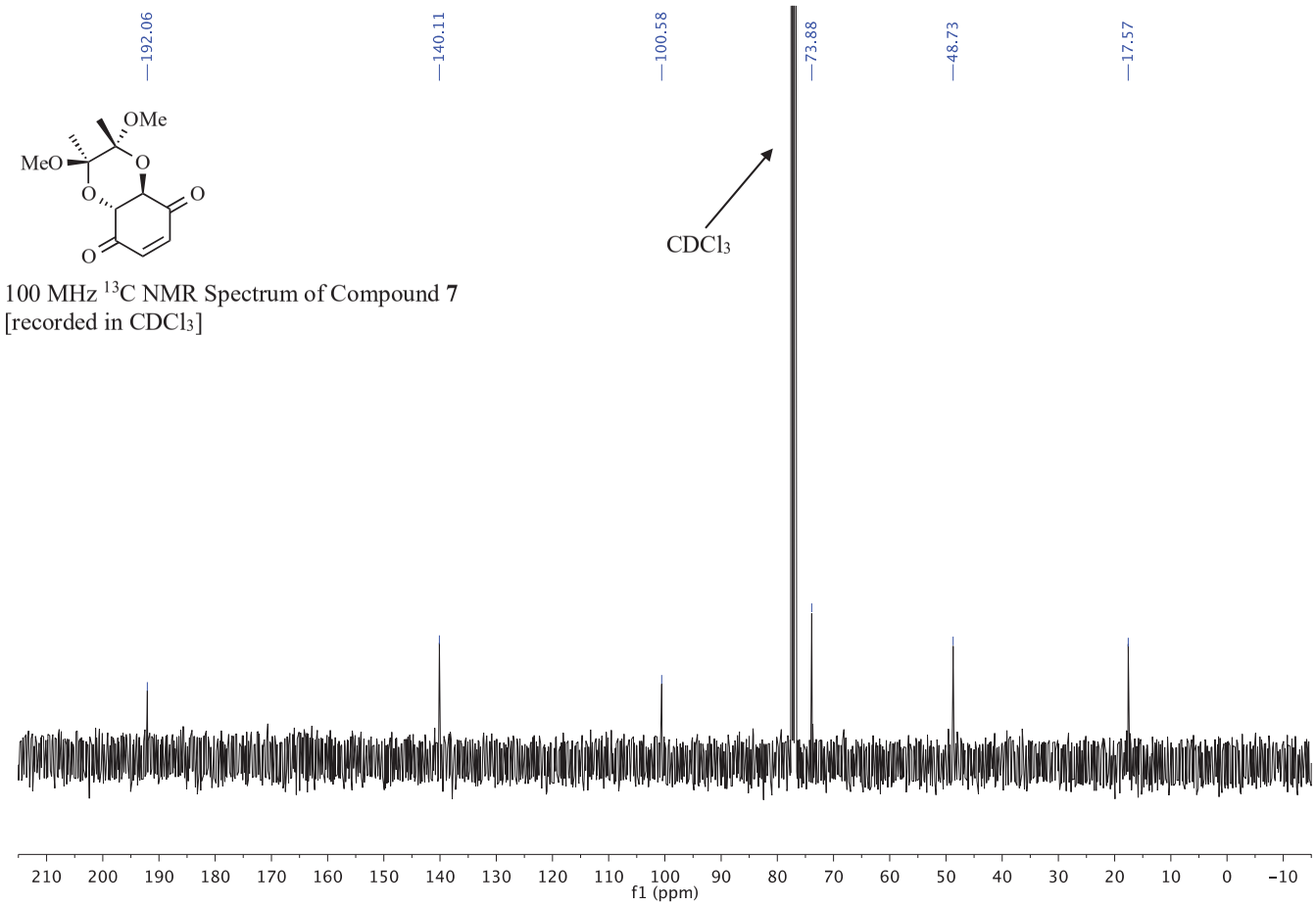
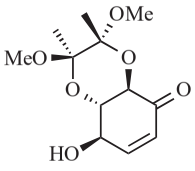

OMe
MeO
O
O
O
O
400 MHz ^{1}H NMR Spectrum of Compound **7**
[recorded in $CDCl_3$]
$CHCl_3$
1.00
0.99
3.21
3.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

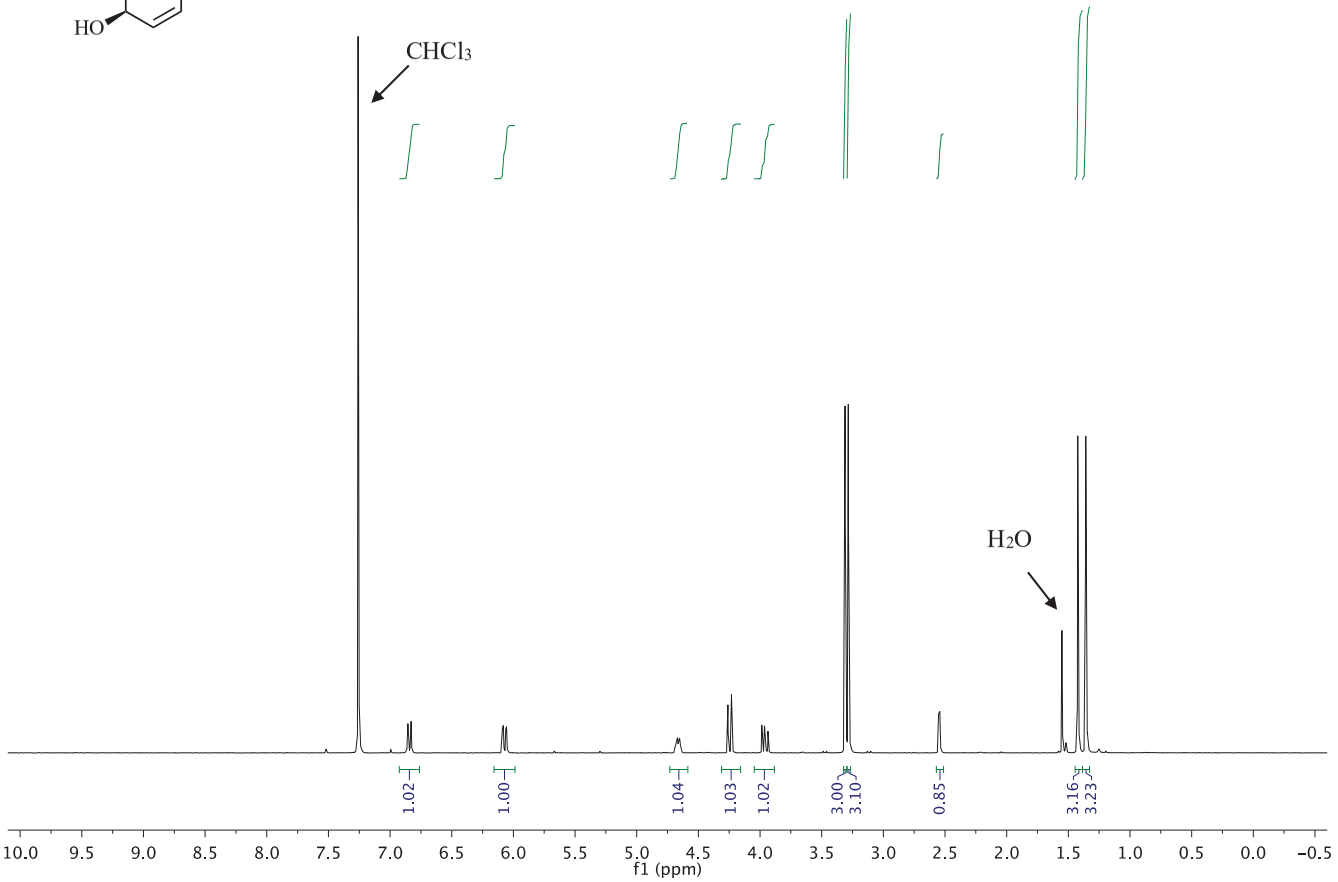


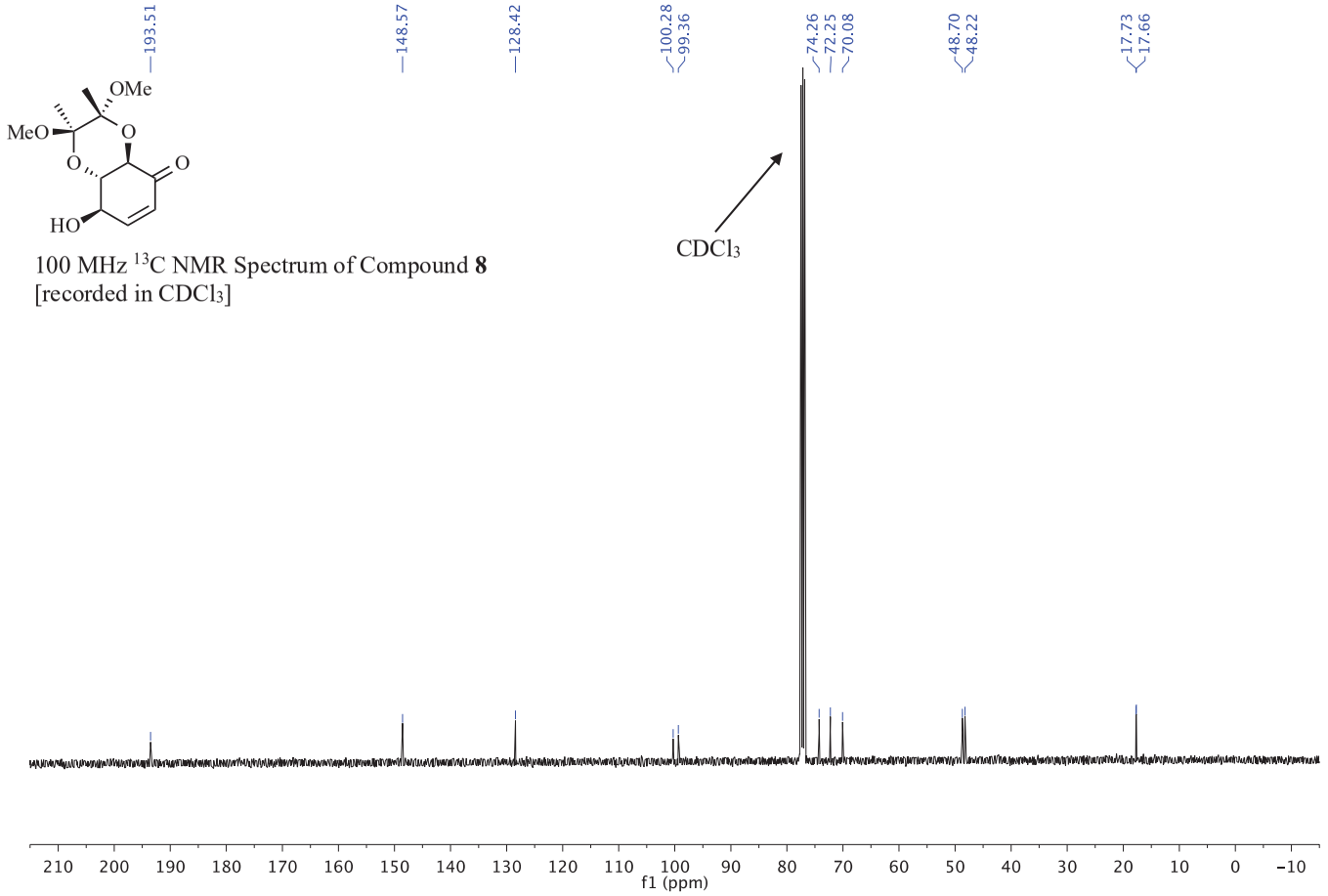
100 MHz ^{13}C NMR Spectrum of Compound **7**
[recorded in $CDCl_3$]

189

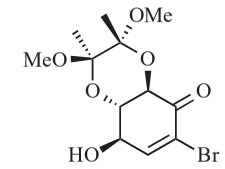


400 MHz ^{1}H NMR Spectrum of Compound **8**
[recorded in $CDCl_3$]

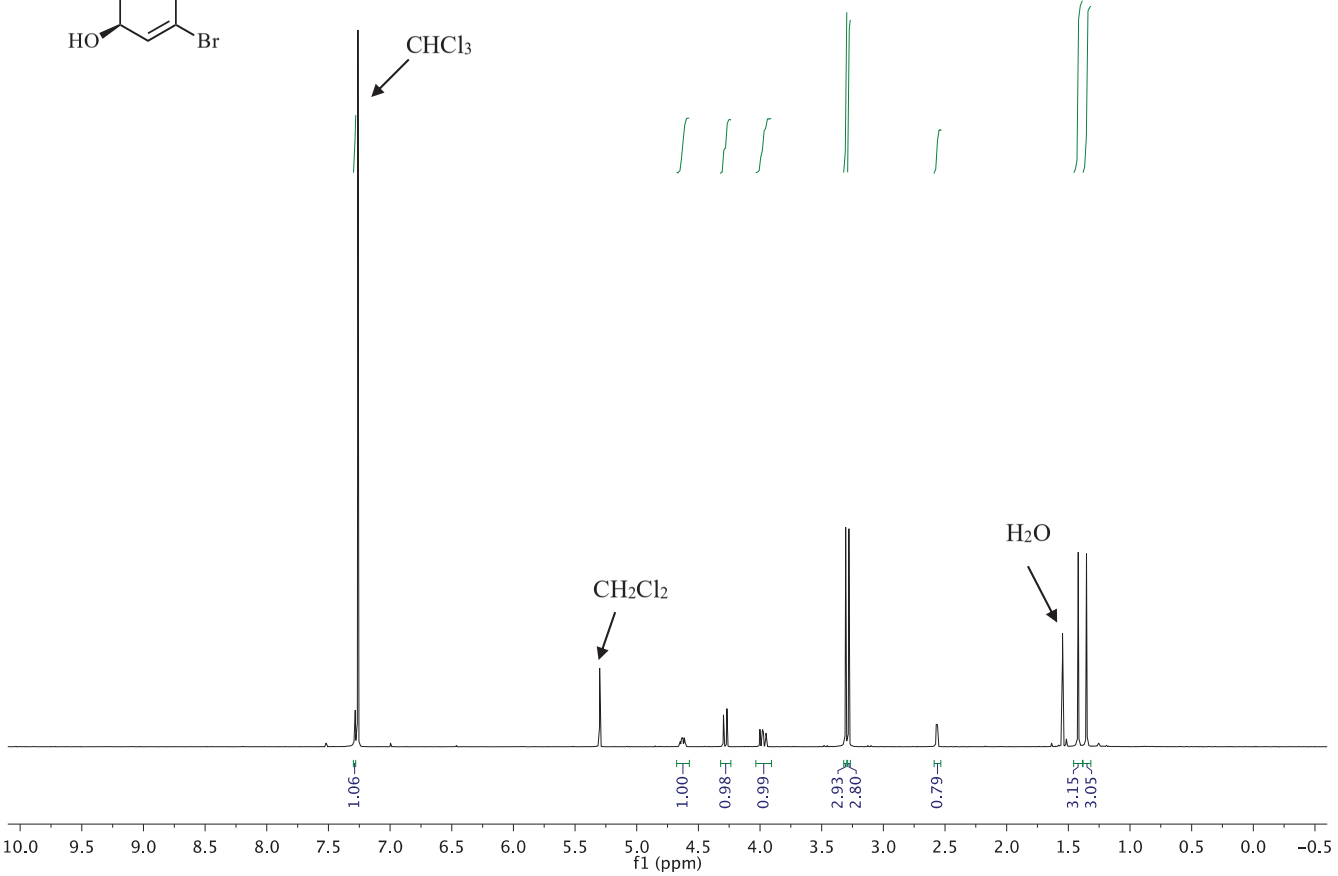


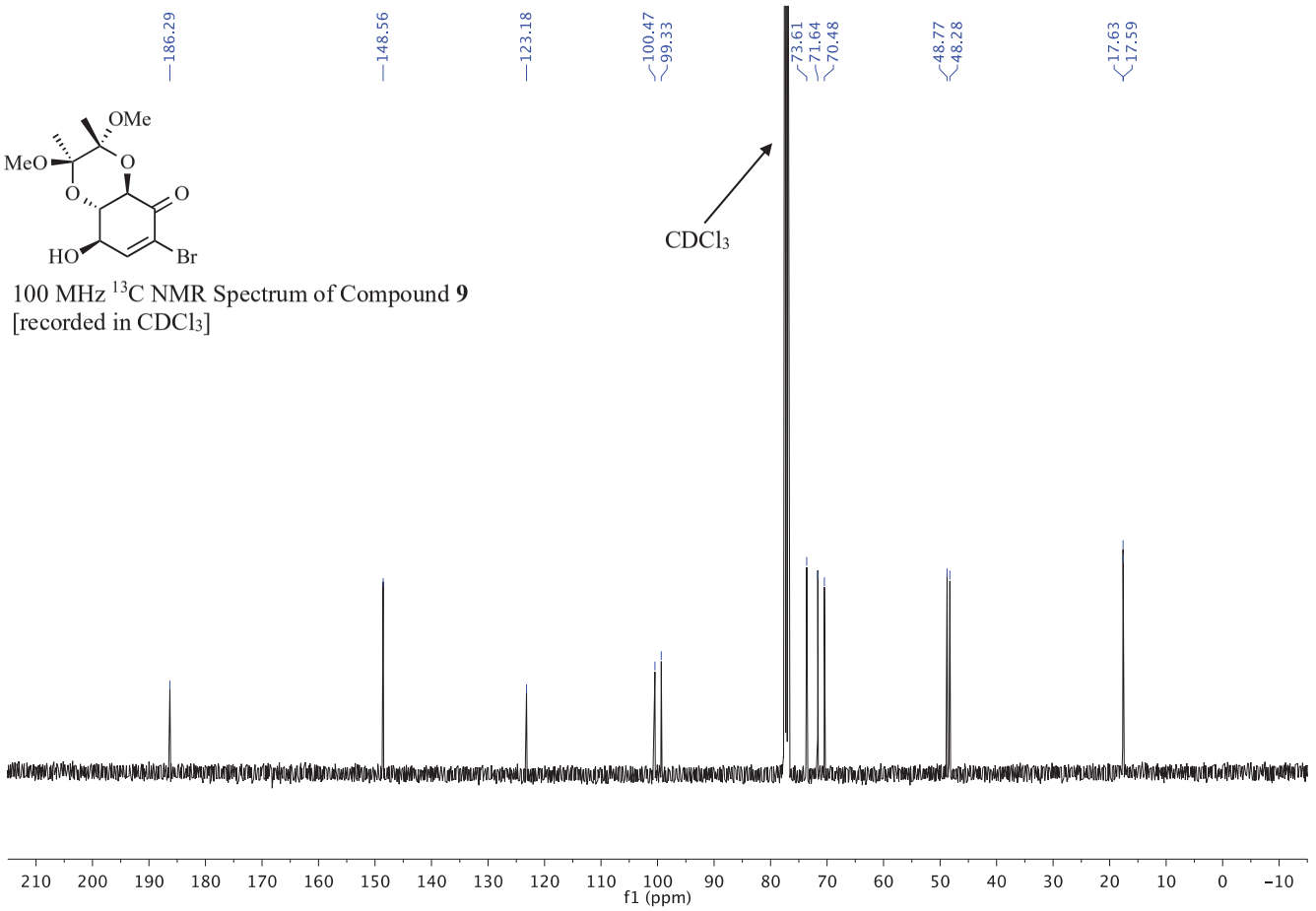


100 MHz ^{13}C NMR Spectrum of Compound **8**
[recorded in $CDCl_3$]

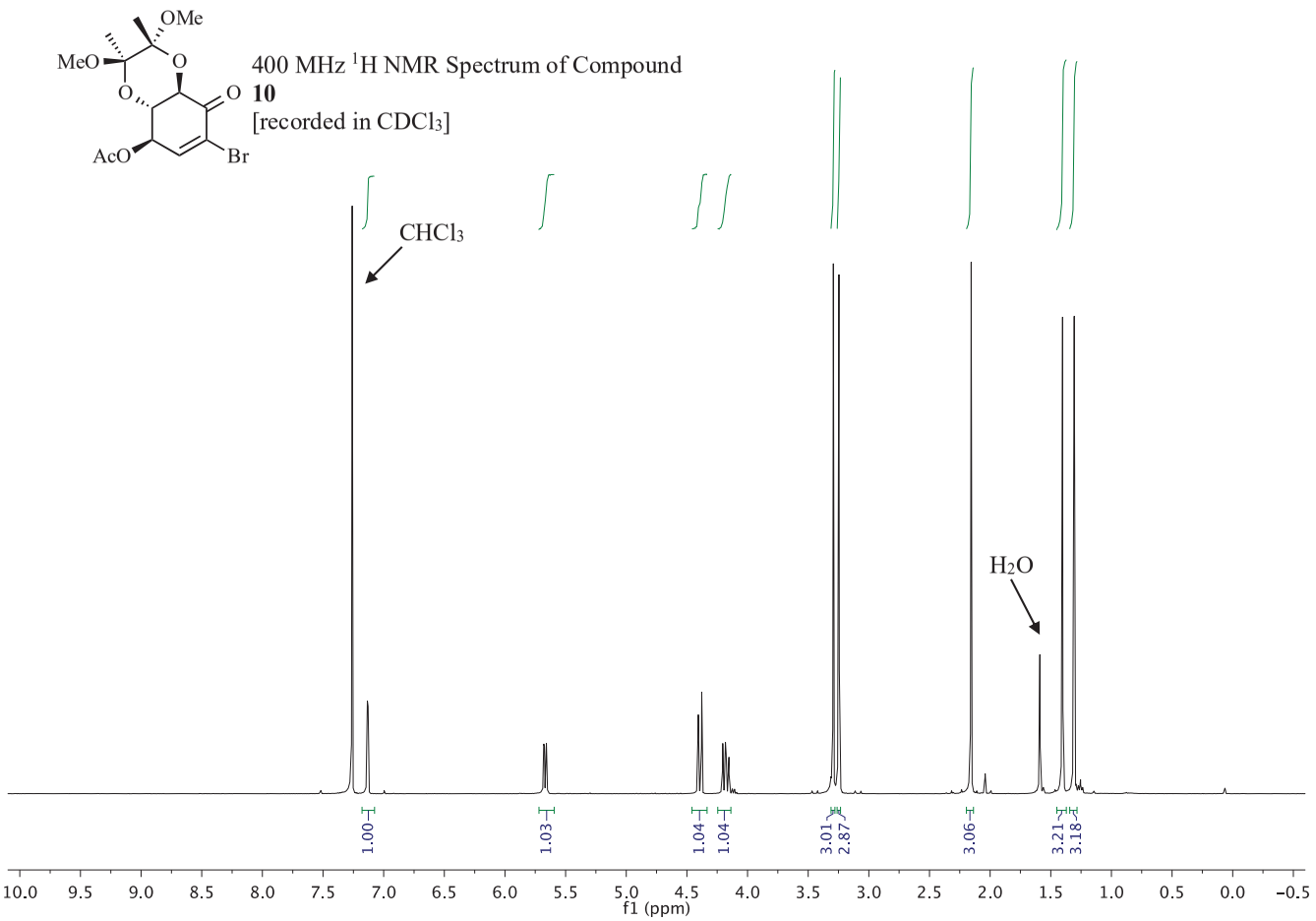


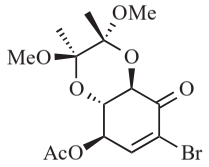
400 MHz ^{1}H NMR Spectrum of Compound **9**
[recorded in $CDCl_3$]



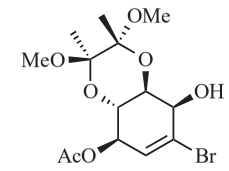


100 MHz ^{13}C NMR Spectrum of Compound **9**
[recorded in $CDCl_3$]

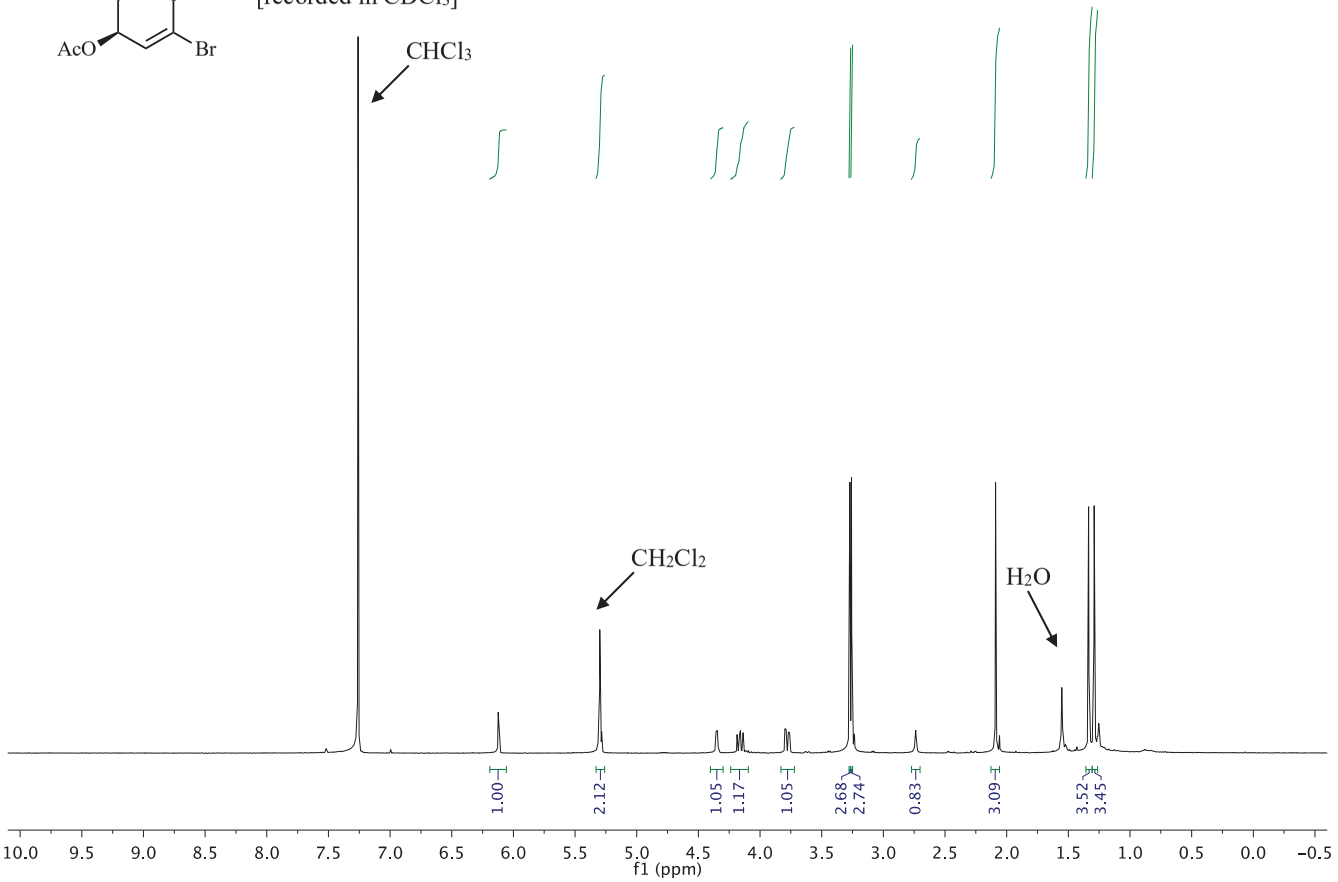

OMe
MeO
O
O
O
AcO
Br
400 MHz ^{1}H NMR Spectrum of Compound
10
[recorded in $CDCl_3$]
$CHCl_3$
H_2O
1.00
1.03
1.04
1.04
3.01
2.87
3.06
3.21
3.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

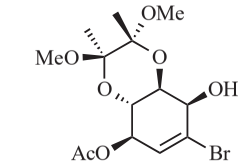


100 MHz ^{13}C NMR Spectrum of Compound
10
[recorded in $CDCl_3$]

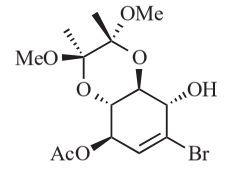


400 MHz ^{1}H NMR Spectrum of Compound
11
[recorded in $CDCl_3$]

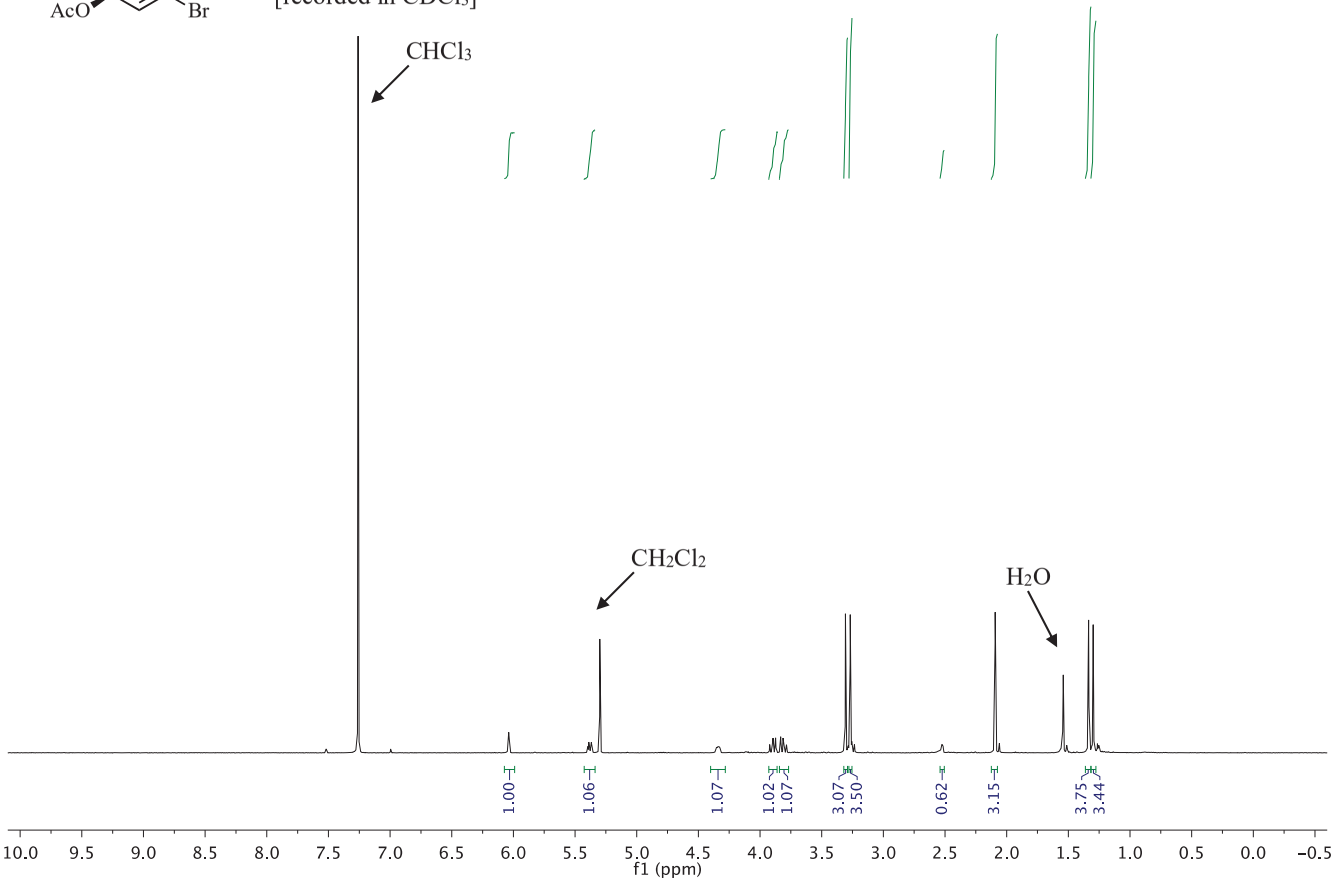


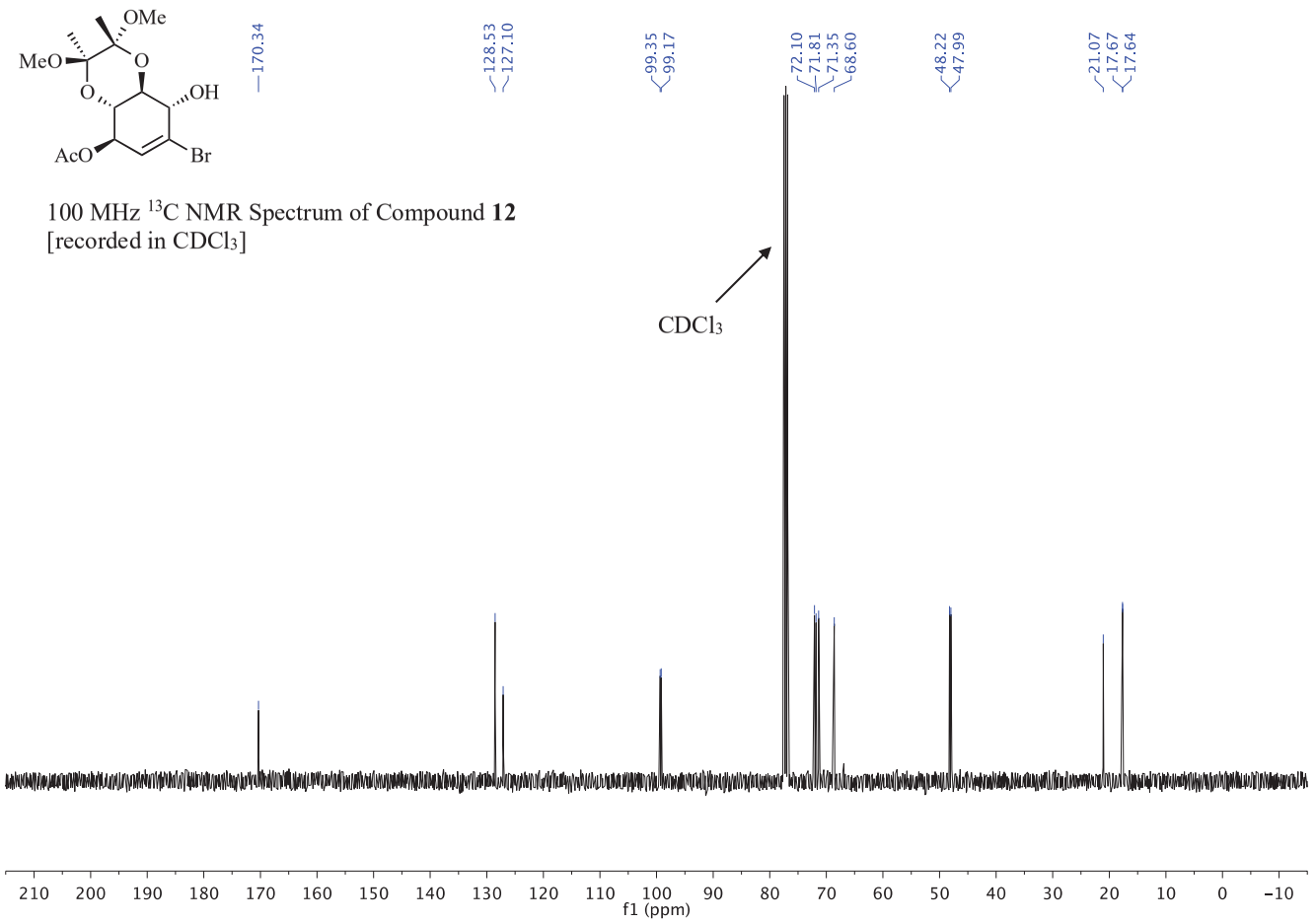


100 MHz ^{13}C NMR Spectrum of Compound **11**
[recorded in $CDCl_3$]

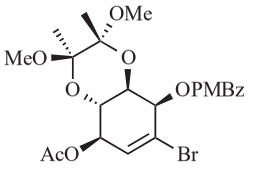


400 MHz ^{1}H NMR Spectrum of Compound
12
[recorded in $CDCl_3$]

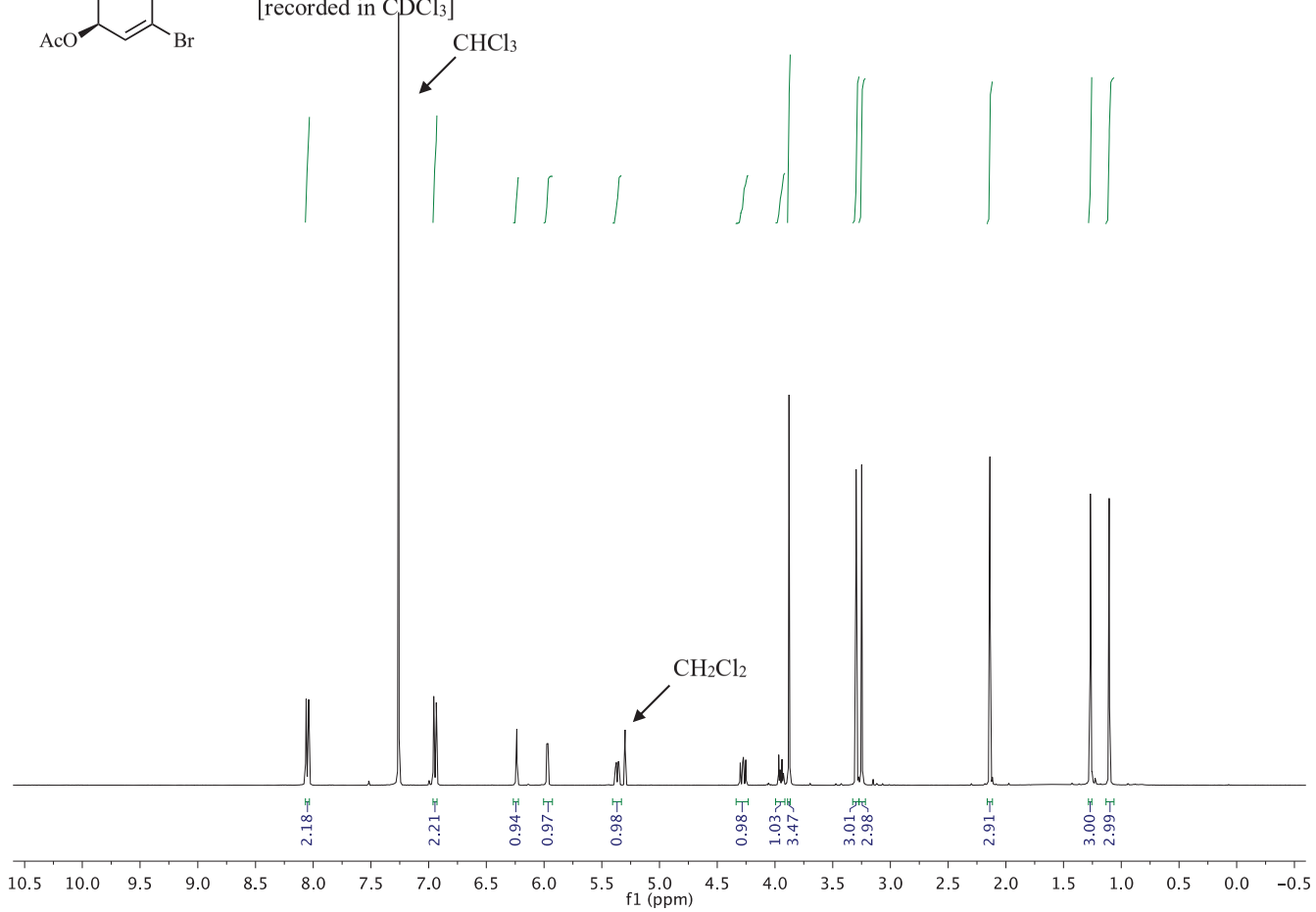




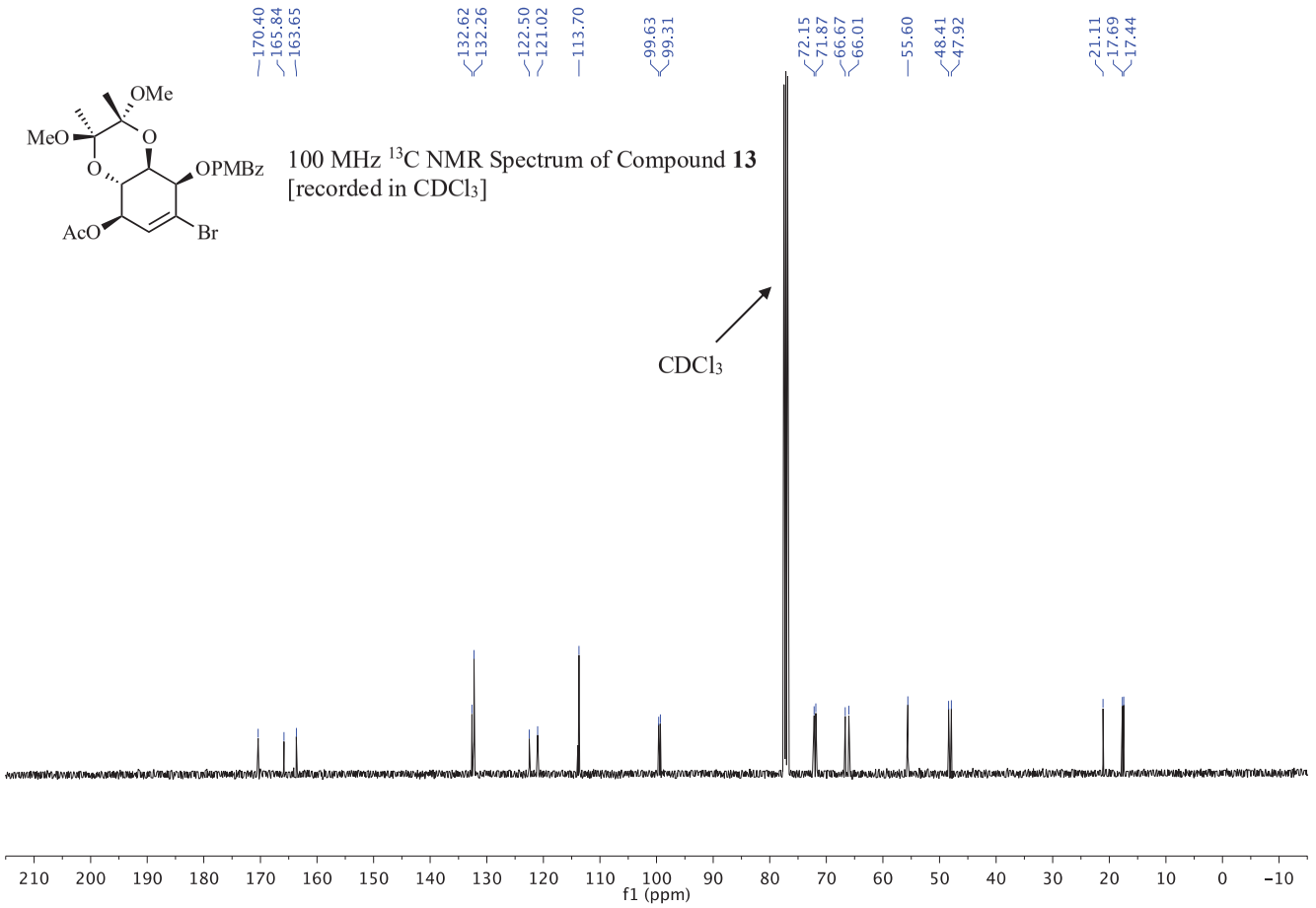
100 MHz ^{13}C NMR Spectrum of Compound **12**
[recorded in $CDCl_3$]

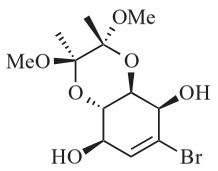


400 MHz ^{1}H NMR Spectrum of Compound **13**
[recorded in $CDCl_3$]

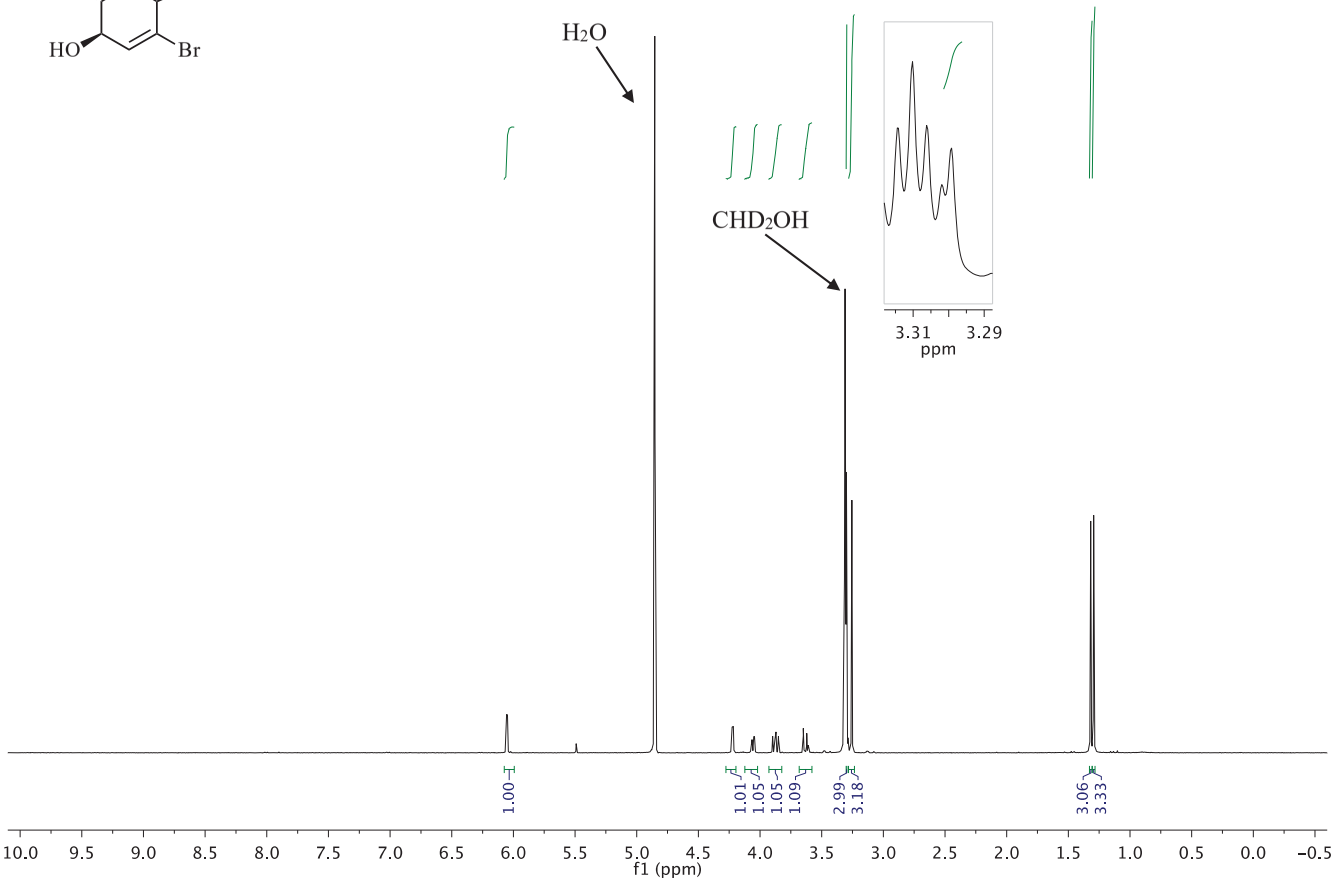


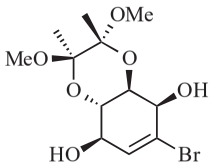
200


170.40
165.84
163.65
132.62
132.26
122.50
121.02
113.70
99.63
99.31
72.15
71.87
66.67
66.01
55.60
48.41
47.92
21.11
17.69
17.44
OMe
MeO
O
O
OPMBz
AcO
Br
100 MHz 13C NMR Spectrum of Compound 13
[recorded in CDCl3]
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



400 MHz ^{1}H NMR Spectrum of Compound *ent*-**1**
[recorded in CD_3OD]





100 MHz ^{13}C NMR Spectrum of Compound *ent*-**1**
[recorded in CD_3OD]

Publication Five

A Total Synthesis of the Cyclic Carbonate-Containing Natural Product Aspergillusol B from *D*-(–)-Tartaric Acid

Joshua N. Buckler, Tamaryn Meek, Martin G. Banwell and Paul D. Carr

Journal of Natural Products, **2017**, *80,* 2088.

JOURNAL OF NATURAL PRODUCTS

Article

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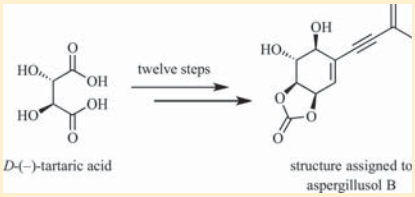
Total Synthesis of the Cyclic Carbonate-Containing Natural Product Aspergillusol B from D-(−)-Tartaric Acid

Joshua N. Buckler, Tamaryn Meek, Martin G. Banwell,* and Paul D. Carr

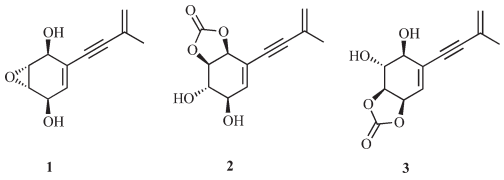
Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

Supporting Information

ABSTRACT: A total synthesis of compound **3** from D-(−)-tartaric acid is reported, thereby establishing that the structure, including relative stereochemistry, originally assigned to the cyclic carbonate-containing natural product aspergillusol B is correct.

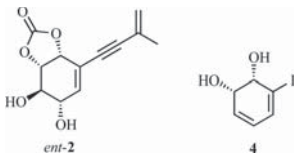


In 2014 Rukachaisirikul and co-workers reported[1] on the isolation and structural elucidation of a series of metabolites from the culture broth of the fungus *Aspergillus* sp. PSU-RSPG185 found in soil samples collected from Surat Thani Province in Thailand. Among these were (+)-asperpentyn (**1**)[2] and two novel cyclic carbonate-containing compounds, named aspergillusols A and B, and to which structures **2** and **3**, respectively, were assigned.[3,4]



1 **2** **3**

The following year we detailed[5] the syntheses of compound **1** and the enantiomer, *ent*-**2**, of the structure assigned to the first of these cyclic carbonates. The enzymatically derived and enantiomerically pure *cis*-1,2-dihydrocatechol **4**[6] was used as the starting material in this work, and by such means we were able to confirm the structures of (+)-asperpentyn (**1**) and aspergillusol A save for the absolute stereochemistry of the latter. This ambiguity arose because of the significant difference in the specific rotation recorded for the synthetically derived compound *ent*-**2** {$[\alpha]_D$ = +192.5 (*c* 0.2, methanol} and that reported for the natural product {$[\alpha]_D$ = −4.6 (*c* 0.49, methanol}.



ent-**2** **4**

Recently, we reported[7] procedures that allow for the conversion of L-(+)-tartaric acid into a range of cyclohexene-based chirons that are likely to have broad applications in chemical synthesis. Of course, the enantiomeric forms of these chirons will be available by using D-(−)-tartaric acid and in order to showcase the utility of our protocols, we now report on their use to prepare, for the first time, compound **3** in enantiomerically pure form from this abundant and enantiomerically pure starting material.

RESULTS AND DISCUSSION

The synthetic route shown in Scheme 1 was used to convert D-(−)-tartaric acid (**5**) into a series of chiral cyclohexenes, and this parallels, exactly, the one employed to make the enantiomeric systems. Thus, compound **5** was treated with a mixture of diacetyl, trimethyl orthoformate, and catalytic amounts of *p*-toluenesulfonic acid monohydrate in hot methanol to give the Ley diacetal **6** in 72% yield. Treatment of a toluene solution of the latter compound with 2 molar equiv of diisobutylaluminum hydride (DIBAl-H) at −78 °C and then with 7 molar equiv of vinylmagnesium bromide afforded, after allowing the reaction mixture to warm to ambient temperatures, a diastereoisomeric mixture of the anticipated bis-allylic alcohols in 85% yield. This mixture was subjected to ring-closing metathesis using Grubbs-II catalyst in dichloromethane at ca. 40 °C and by such means the analogous mixture of cyclohexene diols **8** was obtained in 94% combined yield. Twofold oxidation of this mixture using the Dess−Martin periodinane (DMP) in dichloromethane at 0 °C afforded the corresponding enedione **9** (86% yield). Unsurprisingly, and in keeping with earlier observations, compound **9** was prone to aromatization to the isomeric hydroquinone through a 2-fold enolization process. Accordingly, this centrosymmetric species was immediately reduced with just over 1 molar equiv of the Luche reagent in methanol at −78 °C, thereby delivering the γ-hydroxycyclohexenone **10** completely stereoselectively and in 84% yield. All the of IR, NMR, and mass spectral data acquired on this

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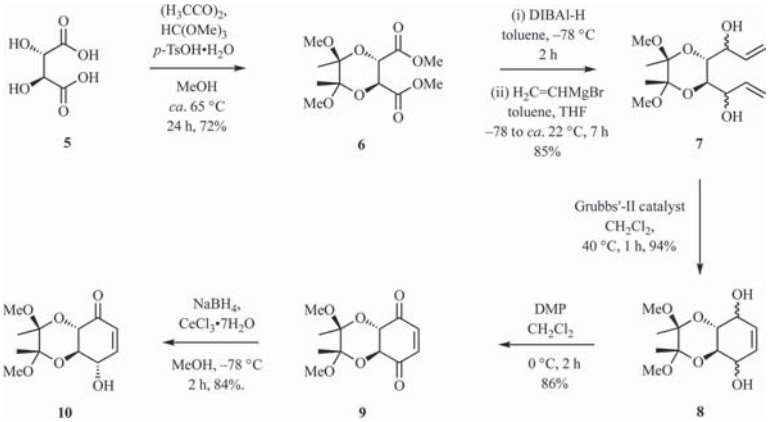
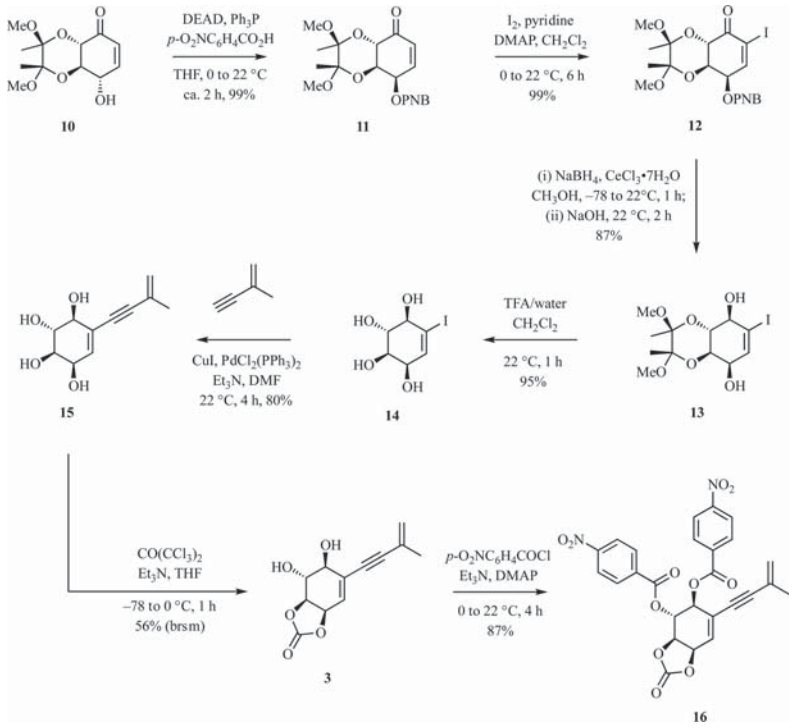
Scheme 1. Elaboration of D-(−)-Tartaric Acid (5) to Homochiral Cyclohexenone Derivatives



Scheme 2. Conversion of Compound 10 into Cyclic Carbonate 3



last compound matched those reported[7] for its enantiomer derived from L-(+)-tartaric acid. Furthermore, the specific rotation of compound **10** was of equal magnitude but opposite sign to that recorded[7] for its enantiomer (viz., *ent*-**10**).

The conversion the γ-hydroxycyclohexenone **10** into the target cyclic carbonate **3** followed the reaction pathway shown in Scheme 2. Thus, the former compound was engaged in a Mitsunobu reaction using *p*-nitrobenzoic acid as nucleophile, and the enone-ester **11** (99%) so-formed subjected to a Johnson α-iodination reaction using molecular iodine and pyridine in dichloromethane in the presence of a catalytic amound of 4-(*N*,*N*-dimethylamino)pyridine (DMAP). By such means compound **12** (99%) was obtained. Luche reduction of enone **12** in methanol at −78 °C proceeded in a completely stereoselective manner and after the intermediate diol monoester was saponified, using aqueous sodium hydroxide, diol **13** was obtained in 87% yield. Cleavage of the Ley diacetal unit within the last compound was achieved using a mixture of trifluoroacetic

DOI: 10.1021/acs.jnatprod.7b00303
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acid (TFA) and water in dichloromethane at 22 °C and by such means the iodocondurtitol **14** (95%) was obtained. Tetra-ol **14** is a known compound but because the reported[8] spectral data did not match those we acquired on this material a single-crystal X-ray analysis was carried out (Figure 1).[9] This served to confirm

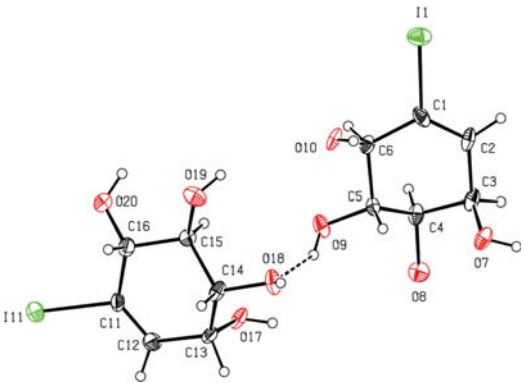

Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **14** (CCDC 1533559) with labeling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii, and the hydrogen-bonding linking the two molecules in the unit cell is shown by a dotted line.

the illustrated structure (including absolute stereochemistry) for compound **14** obtained by the present pathway. Following protocols established in our earlier studies,[5,10] iodide **14** was engaged in a Sonogashira cross-coupling reaction with commercially available 2-methylbut-1-en-3-yne using copper(I) iodide, $PdCl_2(PPh_3)_2$ and triethylamine in dimethylformamide (DMF). In this way the rather insoluble dienyne **15** (80%) was obtained. In the final step of the reaction sequence, compound **15** was treated with bis(trichloromethyl)carbonate (triphosgene) in the presence of triethylamine and using tetrahydrofuran (THF) as solvent. Compound **3** was thereby obtained as a white powder in 26% yield [56% based on recovered starting material (brsm)]. All the spectral data acquired on this cyclic carbonate were in complete accord with the assigned structure. Diol **3** was converted, under standard conditions, into the crystalline bis *p*-nitrobenzoate **16** (87%). While the spectral data acquired on this derivative were also in complete accord with the illustrated structure, all efforts to secure a single-crystal X-ray analysis of this crystalline material were unsuccessful.

A comparison of the spectral data derived from compound **3** with the equivalent data reported[1] for aspergillusol B by Rukachaisirikul and co-workers revealed a very good match (see Table 1). Unfortunately, this group did not report a specific rotation for the naturally derived material. Accordingly, while the absolute stereochemistry of the synthetic material is as illustrated, the corresponding configuration of the natural product cannot be defined at the present time.

CONCLUSIONS

The studies reported herein not only serve to confirm the structure assigned to aspergillusol B but also highlight the capacities of our recently reported protocols[7] to deliver a range of synthetically useful homochiral polyoxygenated cyclohexenes in either enantiomeric form from D- or L-tartaric acid, each of which is an abundant material. Efforts to further demonstrate the utility of such chirons are currently under way in our laboratories and results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ triplet appearing at δ_C 77.1(6) were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on a Perkin−Elmer 1800 Series FTIR spectrometer. Samples were analyzed as either thin films or finely divided solids. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, while

Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 3 with Those Reported[1] for Aspergillusol B

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
aspergillusol B[a]	compound 3[b]	aspergillusol B[c]	compound 3[d]
153.4	153.6	6.06, dd, J = 3.9 and 2.1 Hz, 1H	6.13, br s, 1H
130.2	130.3	5.36, quintet, J = 3.9, and 1.8 Hz, 1H	5.44, br s, 1H
125.7	125.7	5.34, quintet, J = 1.8 Hz, 1H	5.38, br s, 1H
124.5	124.5	5.15, ddd, J = 7.8, 3.9, and 2.1 Hz, 1H	5.21, dd, J = 7.5 and 3.4 Hz, 1H
124.3	124.3	4.64, dd, J = 8.7 and 7.8 Hz, 1H	4.71, apt t, J = 8.5 Hz, 1H
96.7	96.6	4.03, dt, J = 8.7 and 1.8 Hz, 1H	4.09, d, J = 8.4 Hz, 1H
82.5	82.6	4.19, m, 1H	
77.3	77.4	3.76, t, J = 8.7 Hz, 1H	3.83, br t, J = 8.7 Hz, 1H
73.0	72.9[e]	1.88, t, J = 1.2 Hz, 3H	1.95, s, 3H[f]
72.8	72.9[e]		
69.0	69.0		
23.0	23.1		

[a]Data obtained from ref 1, recorded in $CDCl_3$ at 125 MHz. [b]Data recorded in $CDCl_3$ containing 1% $(H_3C)_4Si$ at 100 MHz. [c]Data obtained from ref 1, recorded in $CDCl_3$ at 500 MHz. [d]Data recorded in $CDCl_3$ containing 1% $(H_3C)_4Si$ at 400 MHz. [e]When the ^{13}C NMR spectrum of compound **3** was recorded in slightly acidic $CDCl_3$, these signals appeared as distinct resonances at δ_C 73.2 and 73.0 ppm. [f]Signals due to hydroxy group protons not observed.

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high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin-layer chromatography was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid−ceric sulfate−sulfuric acid (conc)−water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate−potassium carbonate−5% sodium hydroxide aqueous solution−water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[11] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from Sigma−Aldrich, Merck, TCI, Strem, or Lancaster Chemicals and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX, BDH, or Unilab Chemicals. THF, methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[12] Where necessary, reactions were performed under a nitrogen atmosphere.

Synthesis of 1,1′-((2*R*,3*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(prop-2-en-1-ol) (7). The previously reported[13] diester **6** (3.41 g, 11.7 mmol), which is readily derived from D-tartaric acid (**5**), was treated, successively, with di-isobutylaluminum hydride in toluene and then with vinyl magnesium bromide as described[6] for the reaction of compound *ent*-**6**. By such means compound **7** (2.87 g, 85%) was obtained as a mixture of three diastereoisomers. **7**: clear, colorless oil; the ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[7] for the corresponding mixture of enantiomers.

Synthesis of (2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexa-hydrobenzo[*b*][1,4]dioxine-5,8-diol (8). Compound **7** (5.50 g, 19.1 mmol) was subjected to ring-closing metathesis using the Grubbs-II catalyst (in dichloromethane at 40 °C) in the same manner as applied to its enantiomer (*ent*-**7**) and thereby affording cyclohexene **8** (4.68 g, 94%) as a mixture of three diastereoisomers. **8**: white, amorphous solid; the ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[7] for the corresponding mixture of enantiomers.

Synthesis of (2*S*,3*S*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydrobenzo[*b*][1,4]dioxine-5,8-dione (9). Compound **8** (1.26 g, 4.85 mmol) was subjected to 2-fold oxidation using three molar equivalents of DMP in the same manner as employed for its enantiomer (*ent*-**8**) and thus affording enedione **9** (1.07 g, 86%). **9**: bright yellow, crystalline solid, mp 162−165 °C, lit.[7] mp (for enantiomer) 115−117 °C (dec.); $[\alpha]_D$ +115 (*c* 1.1 in $CHCl_3$), lit.[7] $[\alpha]_D$ (for enantiomer) −121.0 (*c* 0.9 in $CHCl_3$); the ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[7] for its enantiomer.

Synthesis of (2*S*,3*S*,4a*S*,8*S*,8a*R*)-8-Hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,8,8a-tetrahydrobenzo[*b*][1,4]dioxin-5(4a*H*)-one (10). Compound **9** (1.74 g, 6.77 mmol) was subjected to reduction under the same conditions as used for its enantiomer (*ent*-**9**), viz. using a slight excess of the Luche reagent, thus producing γ-hydroxyenone **10** (1.47 g, 84%). **10**: white and crystalline solid, mp 171−172 °C; $[\alpha]_D$ +225.5 (*c* 1.0 in $CHCl_3$), lit.[7] $[\alpha]_D$ (for enantiomer) −215.0 (*c* 0.5 in $CHCl_3$); the ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those reported[7] for its enantiomer.

Synthesis of (2*S*,3*S*,4a*R*,5*R*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl 4-Nitrobenzoate (11). A magnetically stirred solution of compound **10** (480 mg, 1.86 mmol), triphenylphosphine (585 mg, 2.23 mmol), and *p*-nitrobenzoic acid (373 mg, 2.23 mmol) in dry THF (40 mL) was cooled to 0 °C then diethyl azodicarboxylate (DEAD) (360 μL, 2.23 mmol) was added over 0.25 h. The resulting solution was stirred at 0 °C for 0.5 h before being allowed to warm to 22 °C then stirred at this temperature for another 1.5 h. The solution thus obtained was concentrated under reduced pressure and the light yellow solid thus obtained was subjected to flash chromatography (silica, dichloromethane → 1:19 v/v diethyl ether/dichloromethane gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:19 v/v diethyl ether/dichloromethane) afforded *p*-nitrobenzoate **11** (750 mg, 99%). **11**: white, crystalline solid, mp 183−185 °C; $[\alpha]^{20}_D$ +156 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.24 (m, 2H), 7.03 (dd, *J* = 10.1 and 5.8 Hz, 1H), 6.26 (d, *J* = 10.1 Hz, 1H), 5.83 (dd, *J* = 5.8 and 3.8 Hz, 1H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.24 (dd, *J* = 11.0 and 3.8 Hz, 1H), 3.37 (s, 3H), 3.27 (s, 3H), 1.43 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 164.4, 150.9, 139.4, 135.5, 133.0, 131.1, 123.8, 100.5, 100.0, 70.3, 67.9, 67.3, 48.8, 48.4, 17.7, 17.6; IR ν_{max} 2980, 1721, 1710, 1610, 1528, 1344, 1278, 1111, 1091, 1027, 721 cm^{-1}; MS (ESI, +ve) *m*/*z* 431 and 430 [(M + Na)$^+$, 20 and 100%]; HRMS calcd for $C_{19}H_{21}NNaO_9$ 430.1114, found 430.1118.

Synthesis of (2*S*,3*S*,4a*R*,5*R*,8a*S*)-7-Iodo-2,3-dimethoxy-2,3-dimethyl-8-oxo-2,3,4a,-5,8,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl 4-Nitrobenzoate (12). A solution of molecular iodine (415 mg, 1.64 mmol) in dichloromethane/pyridine (4 mL of a 1:1 v/v mixture) was added over 0.25 h to a magnetically stirred solution of compound **11** (268 mg, 0.66 mmol) and DMAP (4 mg, 0.03 mmol) in dichloromethane/pyridine (10 mL of 7:3 v/v mixture) maintained at 0 °C. The ensuing mixture was stirred for 16 h at 0 °C and after which time it was allowed to warm to 22 °C. The resulting solution was diluted with ethyl acetate (40 mL) and washed successively with HCl (2 × 10 mL of a 1 M aqueous solution), water (1 × 10 mL) and Na_2SO_3 (2 × 10 mL of a saturated aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 10 mL), and combined organic phases washed with brine (3 × 10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Heptane (20 mL) was added to the ensuing residue and the mixture thus obtained concentrated under reduced pressure (so as to remove any remaining traces of pyridine) to give compound **12** (351 mg, 99%). **12**: white foam; $[\alpha]^{20}_D$ −59.0 (*c* 0.9, $CHCl_3$); R_f 0.6 in 1:19 v/v diethyl ether/dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.23 (m, 2H), 7.81 (d, *J* = 6.2 Hz, 1H), 5.68 (dd, *J* = 6.2 and 3.9 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.24 (dd, *J* = 11.0 and 3.9 Hz, 1H), 3.37 (s, 3H), 3.26 (s, 3H), 1.42 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 164.2, 150.9, 147.3, 135.2, 131.2, 123.8, 110.3, 100.6, 99.9, 69.5, 69.1, 66.8, 48.9, 48.5, 17.6, 17.5; IR ν_{max} 2952, 1718, 1607, 1528, 1342, 1264, 1141, 1101, 1035, 719 cm^{-1}; MS (ESI, +ve) *m*/*z* 588 [(M + methanol + Na)$^+$, 70%], 557 and 556 [(M + Na)$^+$, 25 and 100], 430 (50); HRMS calcd for $C_{19}H_{20}INNaO_9$ 556.0080, found 556.0081.

Synthesis of (2*S*,3*S*,4a*R*,5*R*,8*R*,8a*R*)-6-Iodo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,- 5,8,8a -hexahydrobenzo[*b*][1,4]dioxine-5,8-diol (13). Sodium borohydride (15 mg, 0.40 mmol) was added, in portions over 0.08 h, to a magnetically stirred solution of enone **12** (100 mg, 0.19 mmol) and $CeCl_3{\cdot}7H_2O$ (70 mg, 0.19 mmol) in methanol (5 mL) maintained at −78 °C. After 0.5 h the reaction mixture was allowed to warm to 22 °C and water (0.5 mL) then added dropwise. When evolution of hydrogen gas had subsided (ca. 0.25 h), NaOH (0.5 mL of a 1 M aqueous solution) was added to the reaction mixture and the resulting solution stirred for 2 h at 22 °C then diluted with ethyl acetate (20 mL) and washed with $NaHCO_3$ (2 × 5 mL of a saturated aqueous solution). The combined aqueous washings were extracted with ethyl acetate (3 × 5 mL) and then combined organic layers then washed with brine (3 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, dichloromethane → 1:9 v/v methanol/dichloromethane gradient elution) and concentration of the relevant fractions (R_f = 0.2 in 1:19 v/v methanol/dichloromethane) afforded compound **13** (62 mg, 87%). **13**: white, amorphous solid; $[\alpha]^{20}_D$ +85.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 5.8 and 1.8 Hz, 1H), 4.17−4.04 (complex m, 3H), 3.68 (dd, *J* = 10.8 and 4.1 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 2.57 (br d, *J* = 1.7 Hz, 1H), 2.47 (d, *J* = 4.5 Hz, 1H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 109.5, 99.8, 99.4, 74.5, 68.2, 67.5(1), 67.4(9), 48.3, 48.2, 17.9, 17.7; IR ν_{max} 3429, 2949, 1376, 1115, 1028, 919, 849, 815, 656 cm^{-1}; MS (ESI, +ve) *m*/*z* 409 [(M + Na)$^+$, 100%]; HRMS calcd for $C_{12}H_{19}INaO_6$ 409.0124, found 409.0123.

Synthesis of (1*R*,2*R*,3*S*,4*R*)-5-Iodocyclohex-5-ene-1,2,3,4-tetraol (14). Water (200 μL) then trifluoroacetic acid (200 μL) were added successively to a magnetically stirred solution of compound **13**

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(66 mg, 0.17 mmol) in dichloromethane (3 mL) maintained under a stream of nitrogen at 22 °C. The mixture thus obtained was allowed to evaporate to dryness (ca. 0.25 h), the ensuing residue diluted with dichloromethane (3 mL) and the resulting solution again treated with water (200 μL) then trifluoroacetic acid (200 μL). After evaporation to dryness (ca. 0.25 h) the residue was subjected to flash chromatography (silica, 10:9:1 v/v hexane/ethyl acetate/methanol → 1:8:1 v/v hexane/ethyl acetate/methanol gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:8:1 v/v hexane/ethyl acetate/methanol) afforded compound **14** (44 mg, 95%). **14**: white, crystalline solid, mp = 139−141 °C (from ethyl acetate−hexane), lit. mp[8] 145−149 (from acetone/methanol); $[\alpha]^{20}_D$ −39.5 (*c* 0.6, methanol), lit.[8] $[\alpha]^{20}_D$ −45 (*c* 0.5, methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 6.54 (dd, *J* = 5.3 and 1.2 Hz, 1H), 4.05 (dd, *J* = 5.4 and 4.1 Hz, 1H), 3.82−3.77 (complex m, 2H), 3.55 (m, 1H) (signals due to hydroxy group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 139.5, 109.8, 78.5, 73.4, 72.1, 69.7; IR ν_{max} 3279, 2907, 1618, 1264, 1089, 1066, 1046, 1019, 821 cm^{-1}; MS (ESI, +ve) *m*/*z* 295 [(M + Na)$^+$, 100%]; HRMS calcd for $C_6H_9INaO_4$ 294.9443, found 294.9443.

Synthesis of (1*R*,2*R*,3*R*,4*S*)-5-(3-Methylbut-3-en-1-yn-1-yl)-cyclohex-5-ene-1,2,3,4-tetraol (15). A magnetically stirred mixture of iodide **14** (34 mg, 0.125 mmol) and triethylamine (2 mL) in DMF (1 mL) maintained at 22 °C was degassed by sonication under an atmosphere of nitrogen for 0.5 h, then treated with CuI (5 mg, 0.046 mmol), $PdCl_2(Ph_3P)_2$ (21 mg, 0.030 mmol) and 2-methyl-1-buten-3-yne (150 μL, 1.58 mmol). The resulting solution was stirred at 22 °C for 4 h and then the volatiles were removed under reduced pressure. The residue thus obtained was dissolved in THF (1 mL) and subjected to flash column chromatography (silica, 45:50:5 v/v hexane/ethyl acetate/methanol → 23:70:7 v/v hexane/ethyl acetate/methanol gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:8:1 v/v hexane/ethyl acetate/methanol) afforded compound **15** (50 mg, 80%). **15**: white, amorphous solid; $[\alpha]^{20}_D$ −57.1 (*c* 0.6, methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 6.06 (dd, *J* = 5.2 and 1.8 Hz, 1H), 5.30 (m, 1H), 5.27 (m, 1H), 4.23 (app t, *J* = 4.4 Hz, 1H), 3.85 (dd, *J* = 7.2 and 1.8 Hz, 1H), 3.71 (dd, *J* = 9.8 and 7.2 Hz, 1H), 3.49 (dd, *J* = 9.8 and 4.4 Hz, 1H), 1.91 (app t, *J* = 1.3 Hz, 3H) (signals due to hydroxy group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 134.1, 128.3(3), 128.3(1) 122.5, 92.5, 87.5, 74.4, 73.4, 72.1, 67.6, 23.5; IR ν_{max} 3249, 2883, 1664, 1630, 1608, 1429, 1258, 1092, 1051, 898, 633 cm^{-1}; MS (ESI, +ve) *m*/*z* 443 [(2 M + Na)$^+$, 50%], 233 [(M + Na)$^+$, 100]; HRMS calcd for $C_{11}H_{14}NaO_4$ 233.0790, found 233.0790.

Synthesis of (3a*S*,4*R*,5*S*,7a*R*)-4,5-Dihydroxy-6-(3-methylbut-3-en-1-yn-1-yl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-2-one (3). A magnetically stirred solution of tetraol **15** (37 mg, 0.18 mmol) in THF (2 mL) maintained at −78 °C was treated with triethylamine (90 μL, 0.65 mmol) and then with a solution of triphosgene (27 mg 0.09 mmol) in THF (1 mL). The resulting mixture was stirred at −78 °C for 0.5 h then allowed to warm to 0 °C and stirred at this temperature for another 0.5 h. The suspension thus obtained was poured into ice-cold NH_4Cl (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, hexane → 65:35 v/v hexane/ethyl acetate gradient elution) to afford two fractions, A and B. Concentration of fraction A (R_f = 0.3 in 10:9:1 v/v hexane/ethyl acetate/methanol) afforded compound **3** (11 mg, 26% or 56% brsm). Concentration of fraction B (R_f = 0.1 in 10:9:1 v/v hexane/ethyl acetate/methanol) afforded the starting material **15** (20 mg, 54% recovery). The ^{1}H and ^{13}C NMR spectral data obtained on this material were identical with those derived from an authentic sample. **3**: white powder, mp 115−117 °C (dec); $[\alpha]^{20}_D$ −12 (*c* 0.5, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) see Table 1; IR ν_{max} 3412, 2957, 2922, 2199, 1791, 1628, 1357, 1169, 1046, 889, 772, 727 cm^{-1}; MS (ESI, +ve) *m*/*z* 495 [(2 M + Na)$^+$, 70%], 259 [(M + Na)$^+$, 100], 102 (75); HRMS calcd for $C_{12}H_{12}NaO_5$ 259.0582, found 259.0583.

Synthesis of (3a*R*,4*R*,5*S*,7a*R*)-6-(3-Methylbut-3-en-1-yn-1-yl)-2-oxo-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl Bis(4-nitrobenzoate) (16). A magnetically stirred solution of compound **3** (5.1 mg, 0.022 mmol) and triethylamine (100 μL, 0.72 mmol) in dry dichloromethane (2 mL) maintained at 0 °C was treated sequentially with *p*-nitrobenzoyl chloride (16 mg, 0.086 mmol) and DMAP (one crystal, ca. 0.1 mg). The ensuing mixture was allowed to warm to 22 °C, stirred at this temperature for 4 h then diluted with diethyl ether (5 mL) and quenched with phosphate buffer (5 mL of a 1 M, pH 7 aqueous solution). The separated aqueous layer was extracted with diethyl ether (3 × 1 mL) and the combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light yellow residue thus obtained was subjected to flash chromatography (silica, 7:3 v/v hexane/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.6) gave compound **16** (10 mg, 87%). **16**: white, amorphous solid; $[\alpha]^{20}_D$ +77.7 (*c* 0.5, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.25 (complex m, 4H), 8.21−8.17 (complex m, 2H), 8.17−8.13 (complex m, 2H), 6.39 (dd, *J* = 4.1 and 1.8 Hz, 1H), 5.99 (ddd, *J* = 8.0, 1.8, and 1.3 Hz, 1H), 5.83 (dd, *J* = 8.1 and 8.0 Hz, 1H), 5.43 (ddd, *J* = 7.9, 4.1, and 1.3 Hz, 1H), 5.22 (app p, *J* = 1.3 Hz, 1H), 5.12 (br t, *J* = 1.3 Hz, 1H), 5.09 (dd, *J* = 8.1 and 7.9 Hz, 1H), 1.67 (app t, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 163.4, 152.5, 151.2, 133.9, 133.8, 131.2(4), 131.1(9), 126.9, 126.2, 125.4, 125.1, 123.9(4), 123.9(2), 97.2, 82.4, 74.2, 72.3, 71.0, 68.9, 22.7 (one signal obscured or overlapping); IR ν_{max} 3932, 2852, 1809, 1732, 1607, 1524, 1347, 1259, 1095, 1051, 907, 716 cm^{-1}; MS (ESI, +ve) *m*/*z* 557 [(M + Na)$^+$, 100], 337(70); HRMS calcd for $C_{26}H_{18}N_2NaO_{11}$ 557.0803, found 557.0808.

Crystallographic Studies. *Crystallographic Data.* Compound **14**: $C_6H_9IO_4$, *M* = 272.03, *T* = 150 K, monoclinic, space group $P2_1$, *Z* = 4, *a* = 9.4654(3) Å, *b* = 7.09196(19) Å, *c* = 13.2976(5) Å; *V* = 835.51(5) Å^3, D_x = 2.163 g cm^{-3}, 3355 unique data ($2\theta_{max}$ = 147.8°), *R* = 0.081 [for 3304 reflections with $I > 2.0\sigma(I)$]; R_w = 0.225 (all data), *S* = 1.05.

Structure Determination. Diffraction images for compound **14** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector, and the data extracted using the DENZO/Scalepack package.[14] The structure solution was solved by direct methods (SIR92),[15] then refined using the CRYSTALS program package.[16] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1533559). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00303.

Data derived from the single-crystal X-ray analyses of compound **14**; ^{1}H and ^{13}C NMR spectra of compounds **3** and **11**−**16** (PDF)

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION FOR:

A Total Synthesis of the Cyclic Carbonate-containing Natural Product Aspergillusol B from *D*-(–)-Tartaric Acid

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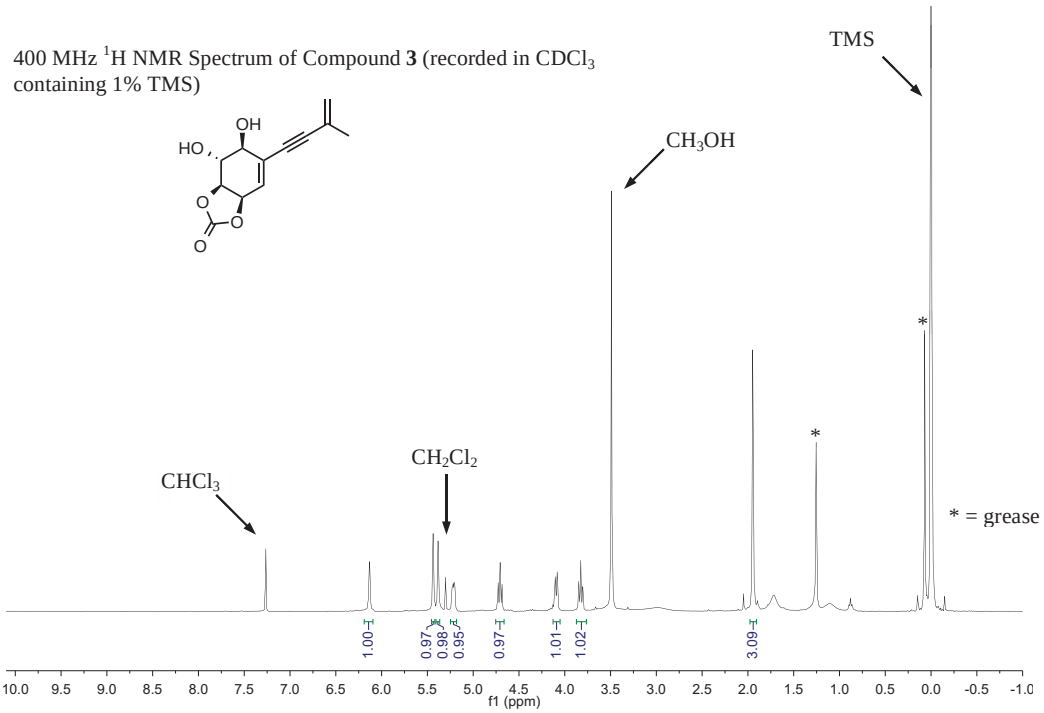
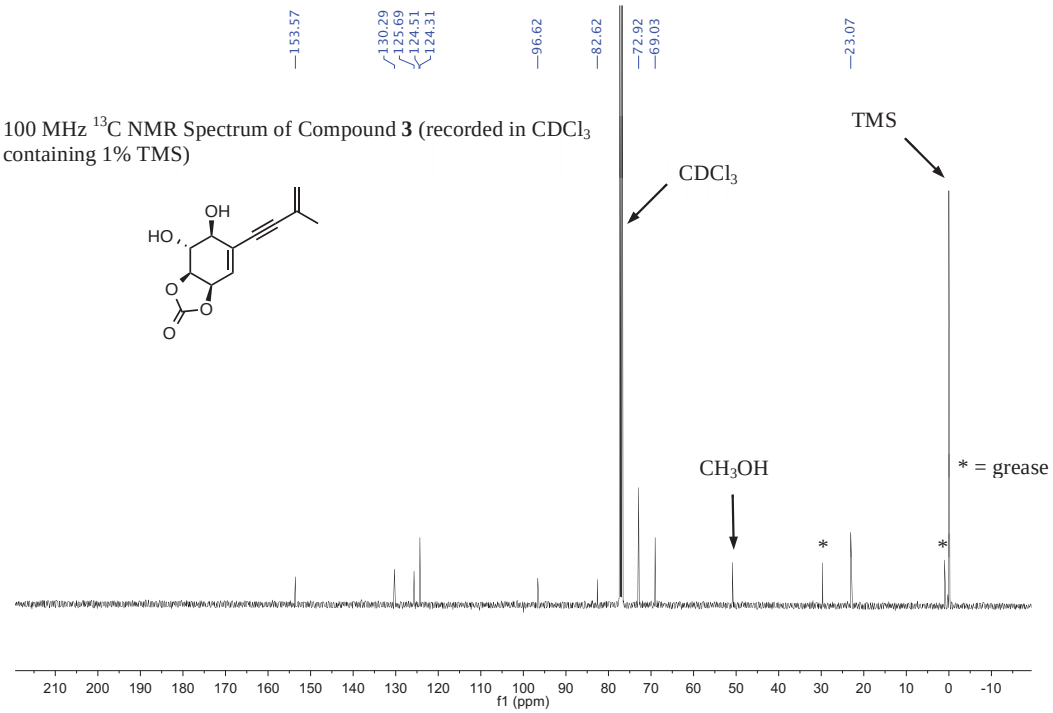
400 MHz ^{1}H NMR Spectrum of Compound **3** (recorded in $CDCl_3$ containing 1% TMS)



100 MHz ^{13}C NMR Spectrum of Compound **3** (recorded in $CDCl_3$ containing 1% TMS)



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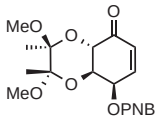

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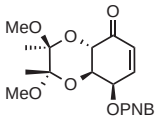

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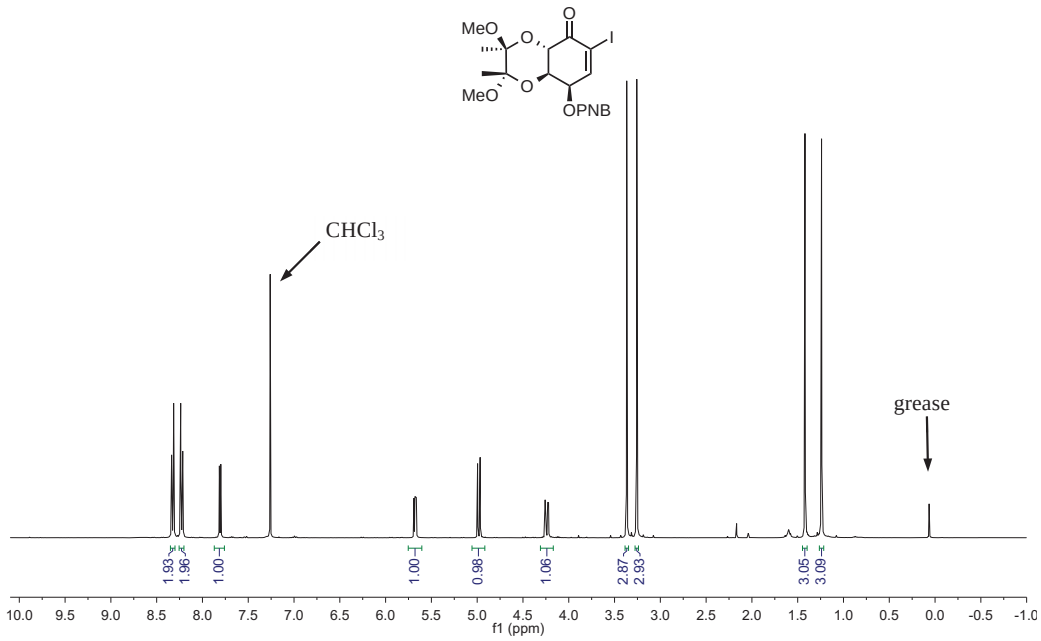

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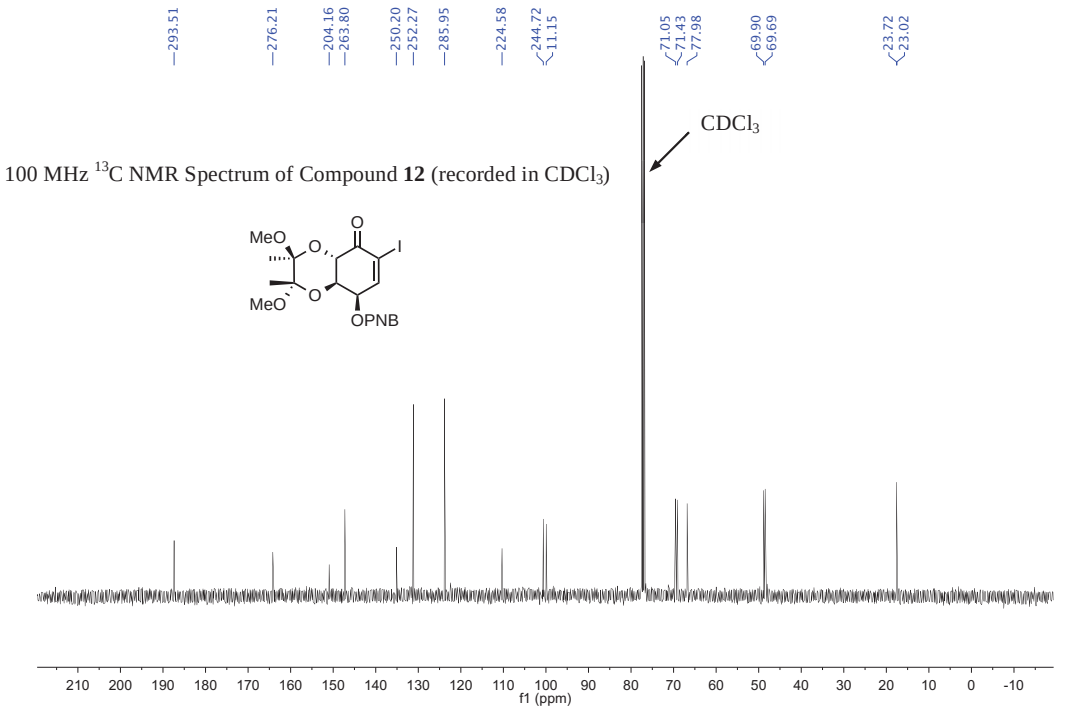

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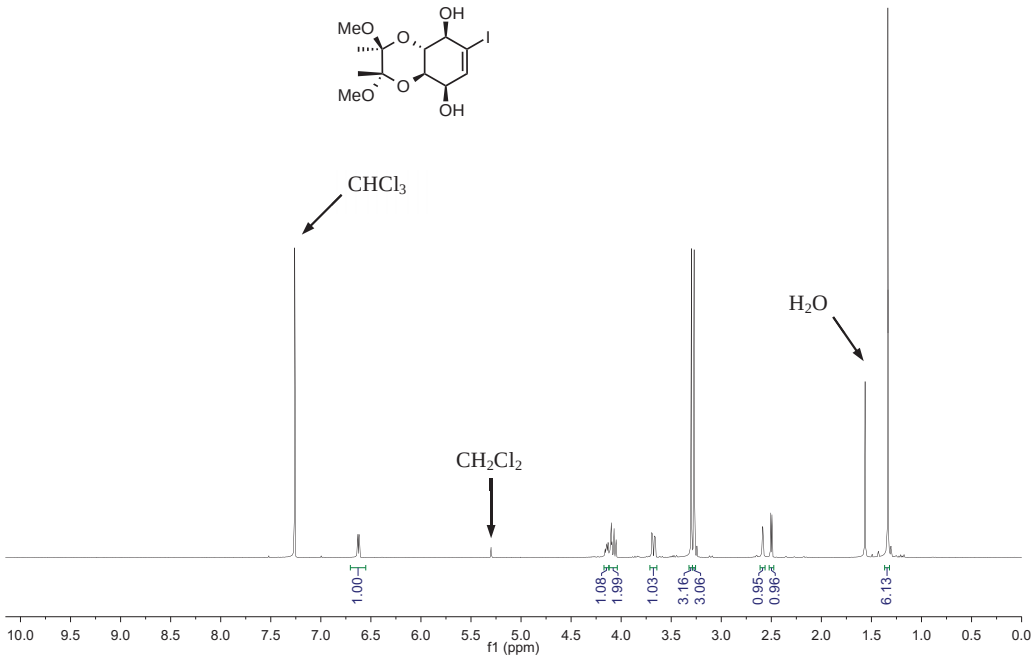

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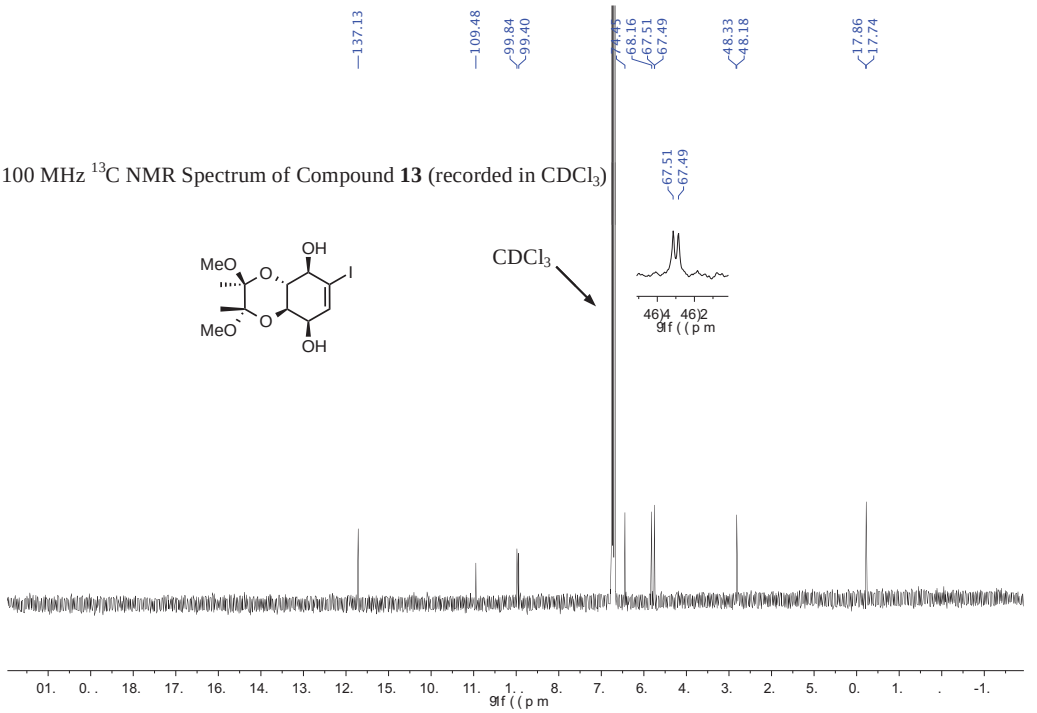

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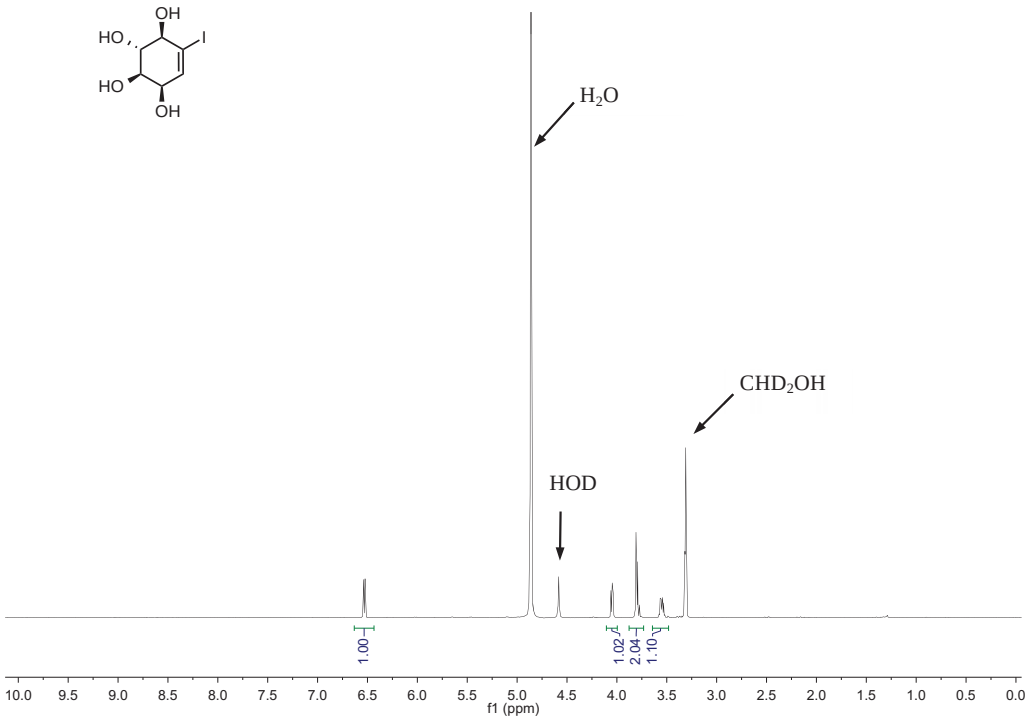

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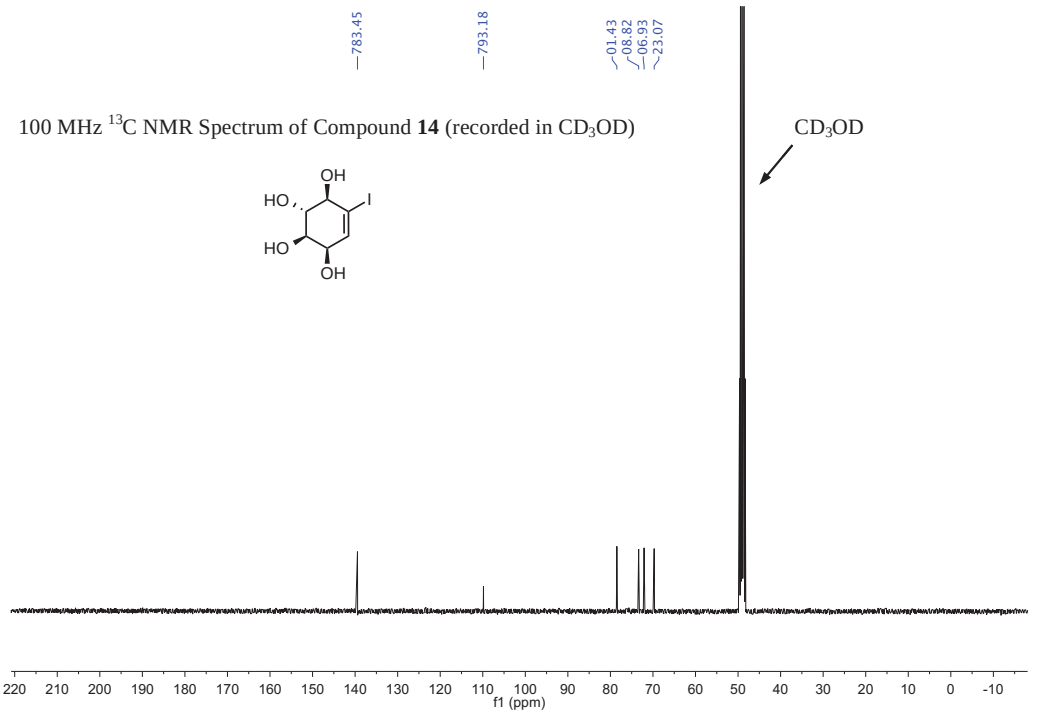

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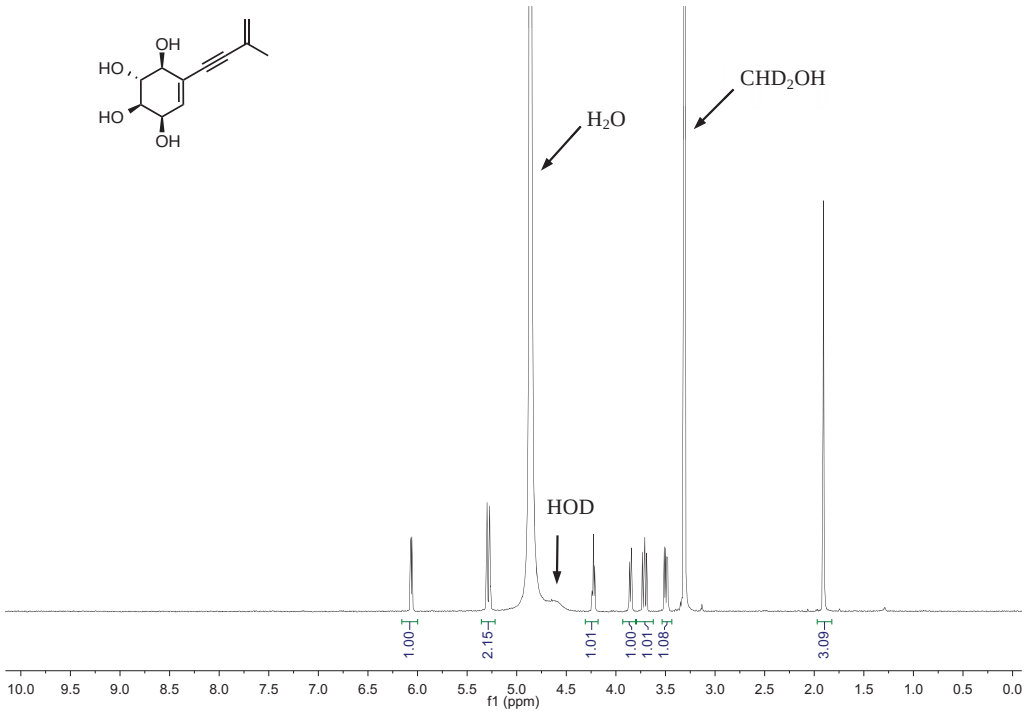

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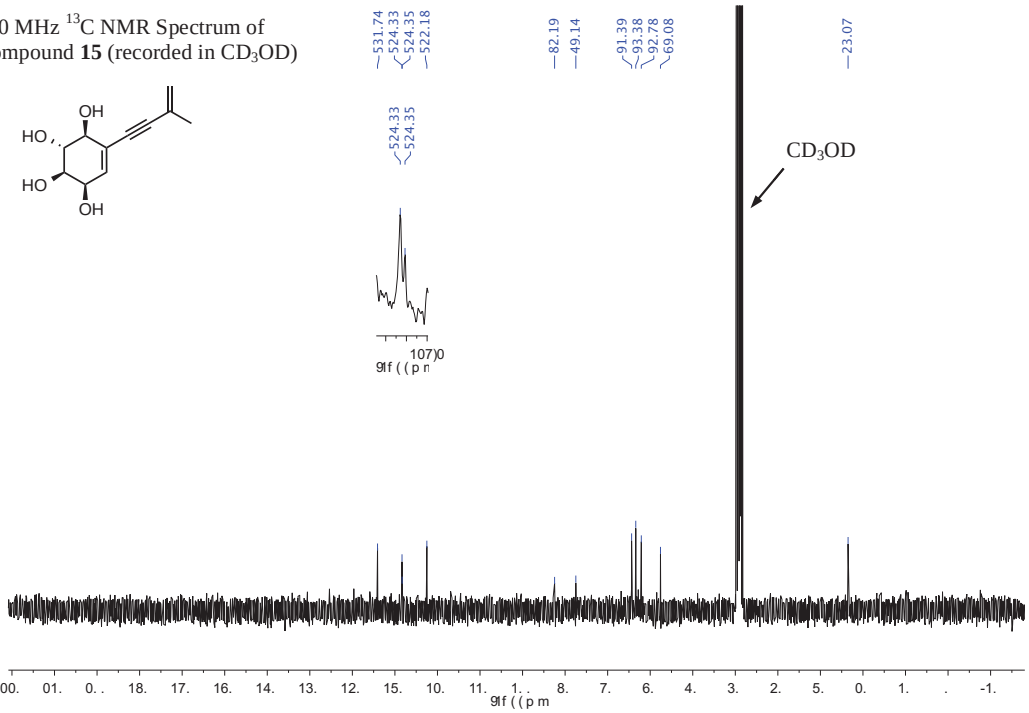

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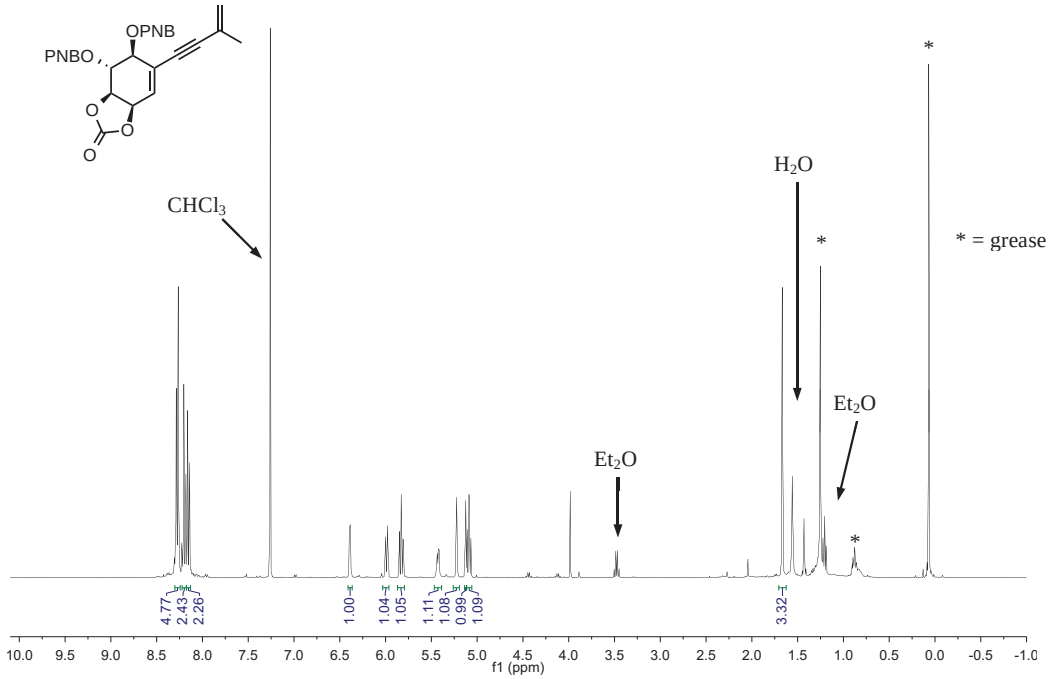
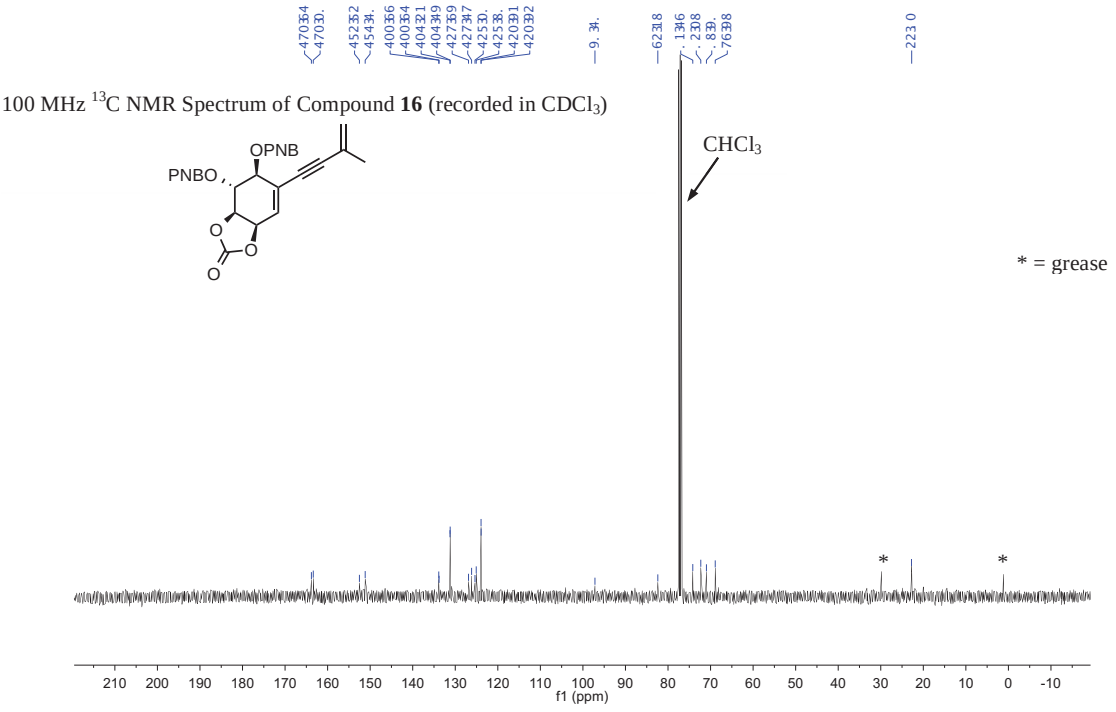


100 MHz ^{13}C NMR Spectrum of Compound **16** (recorded in $CDCl_3$)



Publication Six

Developing Neolignans as Pro-Angiogenic Agents: Stereoselective Total Syntheses and Preliminary Biological Evaluations of the Four Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers

Joshua N. Buckler, Martin G. Banwell, Farzaneh Kordbacheh, Christopher R. Parish, Fernando S. Santiago and Levon M. Khachigian

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Developing Neolignans as Proangiogenic Agents: Stereoselective Total Syntheses and Preliminary Biological Evaluations of the Four Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers

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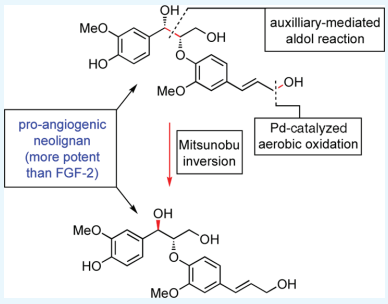
Supporting Information

ABSTRACT: Stereoselective total syntheses of the four stereoisomeric forms of guaiacylglycerol 8-*O*-4′-coniferyl ether, viz., compounds **1**, *ent*-**1**, **2**, and *ent*-**2**, have been established. The key step involves an Evans/Seebach auxiliary-controlled and syn-selective aldol process followed, in the reaction sequences leading to the anti-compounds, by a Mitsunobu reaction involving a benzylic alcohol residue. The proangiogenic properties of the synthetic materials were evaluated in a human microvascular endothelial cell tubule formation assay, thus revealing that they are all active, with the 8S-configured compounds **1** and **2** being the most potent.



INTRODUCTION

Compounds that promote the formation of new blood vessels from existing endothelia are described as proangiogenic and could be beneficial in promoting wound healing, treating burns, and the revascularization of ischemic tissues encountered in stroke victims and those suffering from cardiac disorders.[1] Screening plant extracts for such properties is an emerging area of interest and the rat aortic ring model and related assays have proven useful in identifying natural products that can modulate angiogenesis.[2,3] By such means, various extracts of soybean (particularly the xylem sap) were evaluated recently, and two proangiogenic principals were isolated.[3] Although only small quantities of these materials were obtained, ^{1}H and ^{13}C NMR spectroscopic as well as mass spectral analyses suggested that these are one or other of the neolignans **1** or *ent*-**1** and **2** or *ent*-**2**.[3] The racemic forms of these compounds have previously been isolated from various other plant sources and shown to exhibit a range of biological effects.[4] They are almost certainly produced in vivo through peroxidase-mediated radical coupling of coniferyl alcohol, and optically enriched forms of them (but of undefined absolute stereochemistry) have been generated by enzymatic dehydrogenative coupling of this monomer using cell-free extracts of a producing organism.[5]

Given the very small amounts of these compounds available from natural sources, the seasonal variations in their yields, and the lack of information regarding their stereostructures (and, in many instances, their optical purities), unambiguous syntheses of the guaiacylglycerol 8-*O*-4′-coniferyl ethers **1**, *ent*-**1**, **2**, and *ent*-**2** were sought in an effort to clarify matters. Herein, we detail the total syntheses of each of these four stereoisomeric 8-*O*-4′-linked neolignans[6,7] and report on their proangiogenic properties (Figure 1).

RESULTS AND DISCUSSION

Syntheses of the Racemic Forms of Compounds 1 and 2. Although many neolignans have been the subject of synthetic studies,[8] enantioselective approaches to 8-*O*-4′ linked systems, as required in accessing the compounds targeted here, have received only modest attention.[9,10] Our first approach to compounds **1**, *ent*-**1**, **2**, and *ent*-**2** is shown in Scheme 1, and in this we sought, inter alia, to exploit key elements of Ley's asymmetric synthesis of the 8-*O*-4′ neolignan polysphorin.[9a] This started with the conversion, by conventional means, of commercially available ferulic acid (**3**) over four steps into bis-methoxymethyl (MOM) ether **4** (79%) (see Experimental Section for details). Asymmetric dihydroxylation of the olefinic residue within compound **4** using AD-mix-α and methanesulfonamide afforded the diol **5** (78%), the configuration of which was assigned using the Sharpless "mnemonic".[11] Although the enantiomeric excess (ee) of this oxidation product was not established, the fact that it was optically

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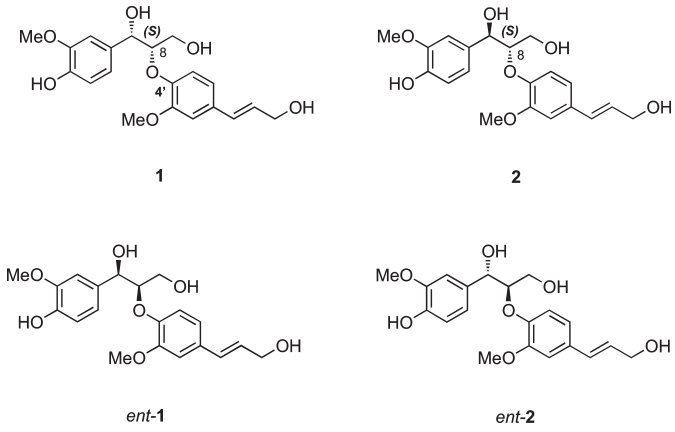
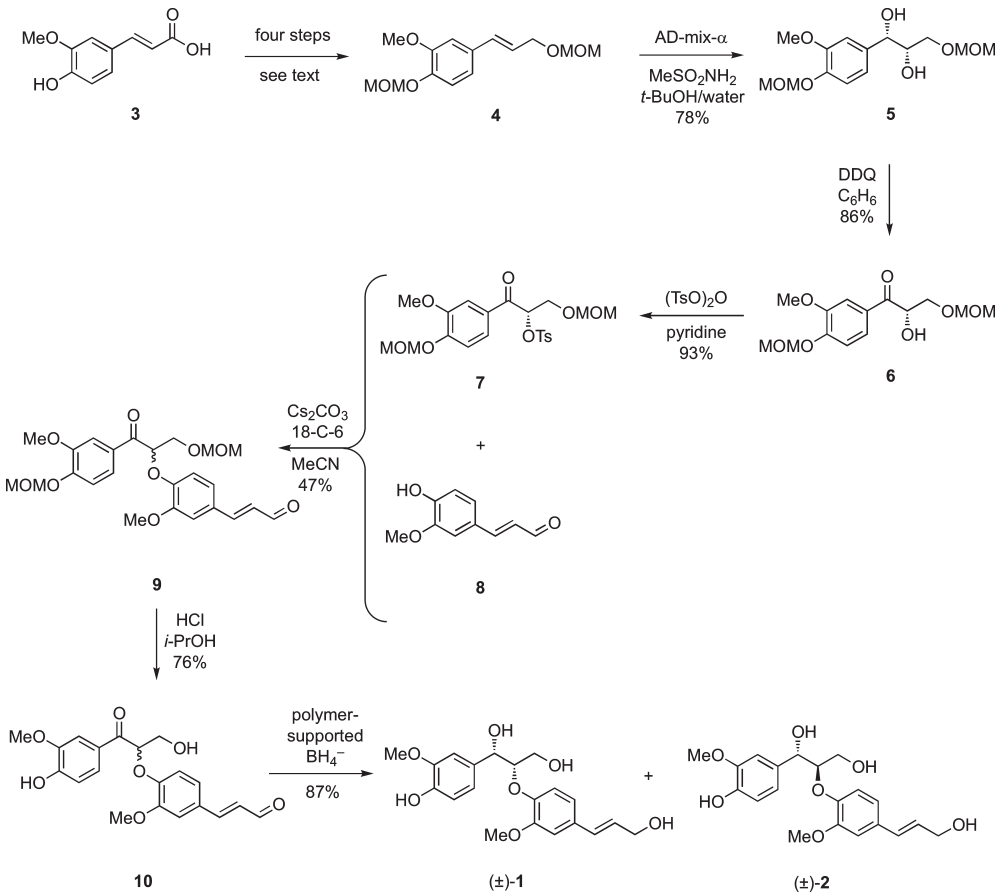


Figure 1. Structures of the four stereoisomeric forms, **1**, *ent*-**1**, **2**, and *ent*-**2**, of guaiacylglycerol 8-*O*-4′-coniferyl ether targeted for synthesis.

Scheme 1. Synthesis of Compounds (±)-1 and (±)-2



active {$[\alpha]_D$ + 10.7 (c = 1.02, $CHCl_3$)} encouraged us to continue exploring the reaction sequence, the next step of which involved selective oxidation of the benzylic hydroxyl group within compound **5** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under ultrasonication conditions.[12] By such means, the acyloin **6** (86%) was obtained and the

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associated hydroxyl group was reacted with *p*-toluenesulfonic anhydride in the presence of pyridine, thus giving the optically active ester **7** in 93% yield. Although treating this last compound with coniferyl aldehyde (**8**) in the presence of cesium carbonate and 18-crown-6 (18-C-6) led to the formation of the anticipated 8-*O*-4′-linked ether **9** (47%), this proved to be an optically inactive material, thus suggesting racemization of substrate **7** and/or the product had occurred under the reaction conditions.[1] Despite this, the completion of the synthetic pathway was pursued because of the capacity it provided to deliver the racemic forms of the target compounds (materials that would prove useful in establishing the enantiomeric excesses of their enantiomerically enriched congeners). So, compound **9** was treated with a trace of concentrated HCl in isopropanol, thus effecting cleavage of the MOM-ether residues, and thereby affording the dihydroxy-derivative **10** (76%). The required 2-fold reduction of the keto-aldehyde **10** was best effected using polymer-supported borohydride[9a] and, in a presumably sterically driven process, this gave a ca. 7:1 mixture of the diastereoisomeric syn- and anti-compounds (±)-**1** and (±)-**2**, respectively, in 87% combined yield. These could be separated from one another using reverse phase high-performance liquid chromatography (HPLC) and the spectral data derived from each were in complete accord with those reported earlier[4e,l] for the natural products (see Table 1 for relevant comparisons of the ^{13}C NMR data sets).

Although each of the synthetically derived compounds (±)-**1** and (±)-**2** could be separated into their constituent enantiomers using chiral HPLC techniques, the equivalent analysis of the soybean-derived natural products could not be carried out due to their decomposition on prolonged (>12 months) standing (as a crude extract). That said, when samples of these compounds have been isolated from other plant sources, they tend to be obtained as racemates or, at best, enantiomerically enriched (but certainly not homochiral) materials.[5a]

Chiral Auxiliary-Controlled Syntheses of Homochiral Compounds 1 and *ent*-1. The synthetic route successfully employed in obtaining neolignan *ent*-**1** is shown in Scheme 2 and involved, as the key feature, an Evans' aldol reaction[13] utilizing the readily available L-valine (**11**)-derived chiral auxiliary **12** introduced by Seebach.[14] This was coupled with the eugenol (**13**)-derived and readily available α-aryloxyacetic acid **14** (85%) through its conversion into the corresponding acid chloride and reaction of this with the anion derived from deprotonation of the 2-oxazolidinone **12** using *n*-butyl lithium. Compound **15** (93%) so formed was then converted, on treatment with dibutylboron triflate in the presence of Hünig's base,[14a] into the corresponding boron enolate that reacted stereoselectively with aldehyde **16** embodying a *tert*-butyldimethylsilyl (TBDMS)-protected phenol residue. The auxiliary associated with the aldol product so-formed was cleaved using lithium borohydride/methanol, thus affording the 1°-alcohol **17** (76% from **15**) as a single diastereoisomer and in optically active form {$[\alpha]_D$ = −63.3 (*c* = 0.8, $CHCl_3$)}. The illustrated structure was initially assigned to compound **17** on the basis of the well-established syn-selective outcomes of Evans' aldol reactions[9h,13,14] involving the types of auxiliaries used here, but eventually it was confirmed through chemical correlation studies (see below). Aerobic and palladium-catalyzed acetoxylation of compound **17** using a procedure reported by Stahl et al.[15] and employing 4,5-diazafluorenone as ligand then afforded ester **18** in 48% yield and exclusively in the E-isomeric form. Cleavage of both the acetate and silyl ether residues associated with compound **18** was accomplished using potassium carbonate in methanol, thus giving the target neolignan *ent*-**1** in 79% yield.

All of the mass spectral as well as the NMR and IR spectroscopic data acquired on compound *ent*-**1** matched those derived from the corresponding racemate [(±)-**1**], and the specific rotation determined for the optically active material was −36.7 (*c* = 0.9, methanol). Chiral HPLC analysis of compound *ent*-**1** established that it was of >99% enantiomeric excess and represents the less mobile component of the racemate (±)-**1**.

The synthesis of compound **1** was readily achieved following the reaction scheme shown above but using the auxilliary *ent*-**12** derived from D-valine (*ent*-**11**). Although all of the spectral data recorded on neolignan **1** matched those reported for its enantiomer, the specific rotation of this material was of similar magnitude but opposite sign {$[\alpha]_D$ = +32.4 (*c* = 0.2, methanol)}. Chiral HPLC analysis of compound **1** established that it had been obtained in ca. 90% ee and represents the more mobile component of the racemate (±)-**1** obtained earlier.

The synthesis of the anti-compound *ent*-**2** is shown in Scheme 3 and involved, in the opening stages, selective mono-protection of the 1°-alcohol residue within compound **17** followed by cleavage of the associated phenolic TBDMS ether.

Table 1. Comparison of the ^{13}C NMR Chemical Shift Data Recorded for Synthetically Derived Compounds (±)-1 and (±)-2 with Those Reported for the Naturally Derived *threo*- and *erythro*-Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers (*threo*-GCCE and *erythro*-GCCE, Respectively)

^{13}C NMR data for compound (±)-**1** (δ_C)[a]	^{13}C NMR data for *threo*-GCCE (δ_C)[b]	Δδ	^{13}C NMR data for compound (±)-**2** (δ_C)[c]	^{13}C NMR data for *erythro*-GCCE (δ_C)[d]	Δδ
151.6	151.8	−0.2	151.9	151.8	+0.1
149.1	149.3	−0.2	148.9	149.0	−0.1
148.8	148.8	0.0	148.7	148.6	+0.1
147.1	147.2	−0.1	147.0	147.2	−0.2
133.7	133.8	−0.1	134.1	134.2	−0.1
133.1	133.2	−0.1	133.0	133.1	−0.1
131.4	131.5	−0.1	131.4[e]	130.8	+0.6[f]
128.6	128.7	−0.1	128.5	128.6	−0.0
120.8	120.9	−0.1	121.0	121.1	+0.1
120.7	120.8	+0.1	120.7	120.8	−0.1
118.6	118.9	−0.3[f]	118.9	119.0	−0.1
115.8	115.9	−0.1	115.7	115.7	0.0
111.7	111.8	−0.1	111.9	111.9	0.0
111.2	111.3	−0.1	111.4[g]	110.8	+0.6[f]
87.0	87.2	−0.2	86.2	86.3	−0.1
74.0	74.1	−0.1	74.1	74.2	−0.1
63.7	63.8	−0.1	63.8	63.9	−0.1
61.9	62.0	−0.1	62.2	62.3	−0.1
56.6	56.6	0.0	56.5	56.6	−0.1
56.3	56.4	−0.1	56.4	56.6	−0.2

[a]Spectrum recorded in CD_3OD at 100 MHz. [b]Data obtained from Woo,[41] spectrum recorded in CD_3OD at 125 MHz. [c]Spectrum recorded in CD_3OD at 100 MHz. [d]Data obtained from Li[4e] spectrum recorded in CD_3OD at 100 MHz. [e]Lourith et al. report[10] a chemical shift of 131.5 for the resonance due to this carbon. [f]We attribute these differences to variations in the pH of the media in which the spectra were recorded. [g]Lourith et al. report[10] a chemical shift of 111.4 for the resonance due to this carbon.

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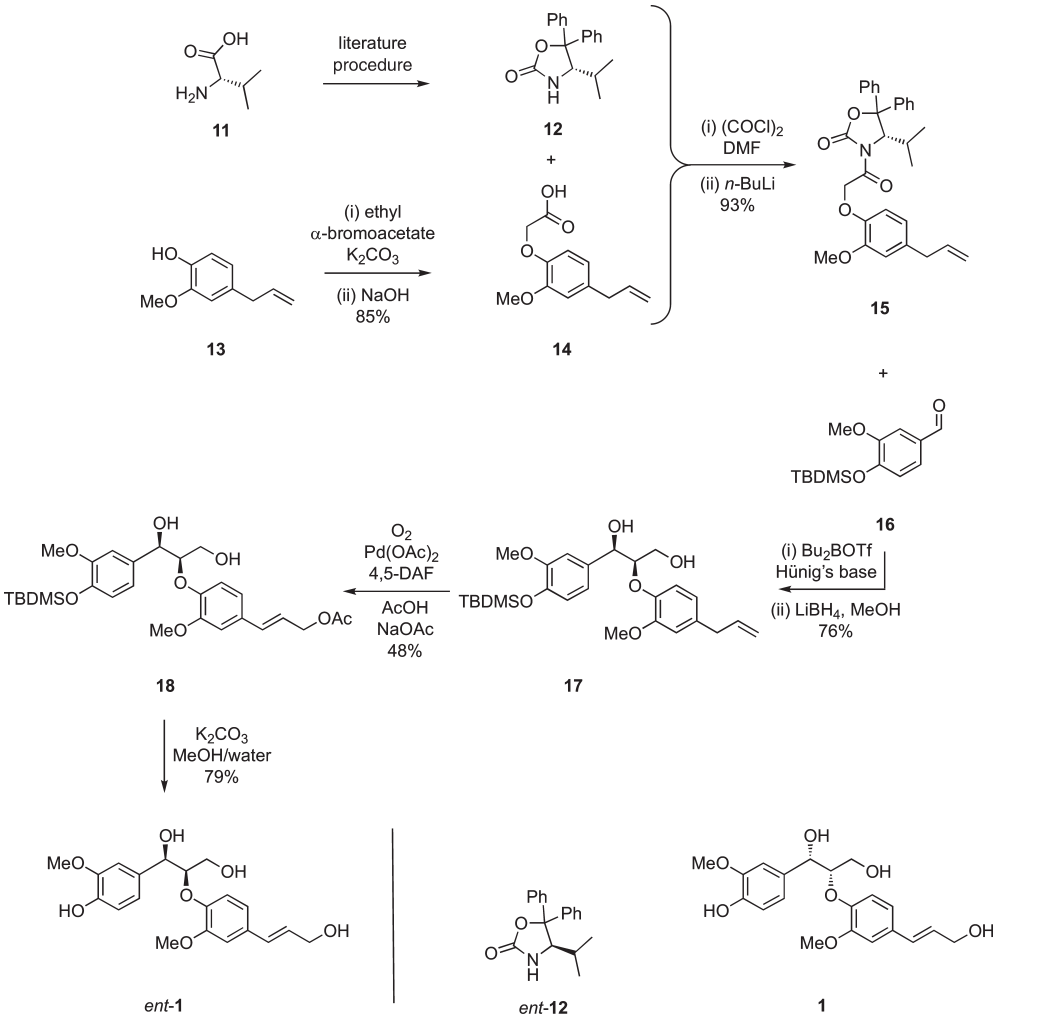
Scheme 2. Synthesis of Compound *ent*-1



This gave phenol **19** (96%) that was reacted with *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to afford ester **20** (87%). The introduction of the tosyl group was necessary to attenuate the electron-donating properties of the attached aryl oxygen such that this now did not facilitate ionization of activated forms of the benzylic alcohol during the subsequent Mitsunobu reaction.[16] Consistent with such expectations, when compound **20** was treated with triphenylphosphine and diethyl azodicarboxylate (DEAD), and using *p*-nitrobenzoic acid as nucleophile, benzoate **21** (84%) was obtained. Confirmation of the illustrated S-configuration at the PNB-ester bearing center in this product follows from its conversion into the target neolignan *ent*-**2**. To such ends, treatment of compound **21** with sodium hydroxide in tetrahydrofuran (THF)/water afforded the alcohol **22** (74%) that was itself subjected to allylic oxidation using Stahl's protocol,[15] thereby affording acetate **23** in 64% yield.

Treatment of ester **23** with tetra-*n*-butylammonium fluoride (TBAF) then sodium hydroxide in water/methanol resulted in cleavage of the TBDMS ether, acetate, and tosyl groups such that the targeted neolignan *ent*-**2** was obtained in 73% yield. All of the spectral data obtained on this material were consistent with the assigned structure. Chiral HPLC analysis established that it was of >99% ee. The specific rotation of this material was $[\alpha]^{20}_{D} = -8.1$ (c = 1.1, methanol), and it represents the more mobile component of the racemate (±)-**2**.

The synthesis of compound **2** was readily achieved following the reaction scheme shown but using compound *ent*-**17** as starting material. Although all of the spectral data recorded on neolignan **2** matched those reported for its enantiomer, the specific rotation of this material was of similar magnitude but opposite sign {$[\alpha]^{20}_{D} = +7.4$ (c = 0.5, methanol)}. Similarly, chiral HPLC analysis of compound **2** established that it was of >99% ee and that it represents the less mobile component of the racemate (±)-**2** obtained as described above.

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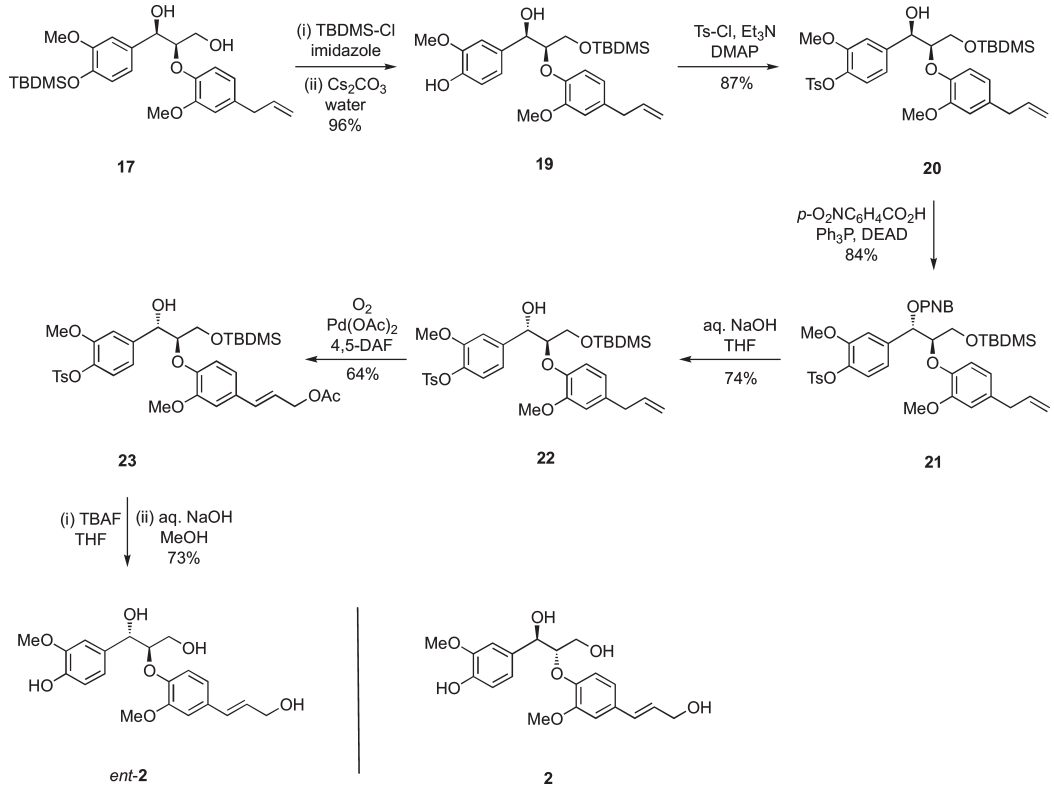
Scheme 3. Synthesis of Compound *ent*-2



To this point, the assignments of the illustrated structures to compounds **1**, *ent*-**1**, **2**, and *ent*-**2** are based on the assumption that the pivotal Evans' aldol reactions proceed in the anticipated (syn-selective) manner and that the Mitsunobu reactions take place with inversion of configuration. Further support follows from the recent work of Nair et al.,[9k] who employed closely related Evans' aldol protocols to prepare compound **2** and who undertook certain chemical correlation studies and a single-crystal X-ray analysis to establish the selectivities of their pivotal reaction. The NMR spectroscopic data we acquired on compound **2** matched those reported by Nair.[9k]

Initial Biological Evaluations of Compounds 1, *ent*-1, 2, and *ent*-2. Compounds **1** and **2** as well as their enantiomers, *ent*-**1** and *ent*-**2**, respectively, were each examined for their abilities to enhance endothelial cell tubule formation on reconstituted basement membrane matrix (see Figure 2 and the Experimental Section) in an assay widely used to identify proangiogenic and antiangiogenic factors and their underlying mechanism(s) of action.[17]

All four compounds stimulated endothelial cell tubule formation compared with media only, with compounds **1** and **2** being the most active and congener *ent*-**2** the least active. It is noteworthy that each of these neolignans exhibited significant proangiogenic activity compared with media only, with compound **1** being more active than the fibroblast growth factor 2 (FGF-2) control.[18] The flavone derivative PD98059, an inhibitor of mitogen-activated protein kinase (MEK1/2) and FGF-2 signaling, suppressed the proangiogenic activity of all of the compounds, which is consistent with the title neolignans acting via this pathway.

■ CONCLUSIONS

The work detailed here provides stereochemically unambiguous routes to a quartet of neolignans that display varying degrees of activity as proangiogenic agents. The variation in efficacy as a function of stereochemistry indicates that the S-configuration at C8 (as seen in neolignans **1** and **2**) has a positive impact on activity, with compound **1** being even more active than the FGF-2 control. To the best of our knowledge, this work represents the first time that a suite of diastereisomerically related neolignans has been identified as proangiogenic agents. As such, it should serve as an important consideration for the development of proangiogenic compounds that might serve as therapeutic agents.

■ EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ triplet appearing at δ_C 77.1(6) were used to reference ^{1}H and ^{13}C NMR spectra,

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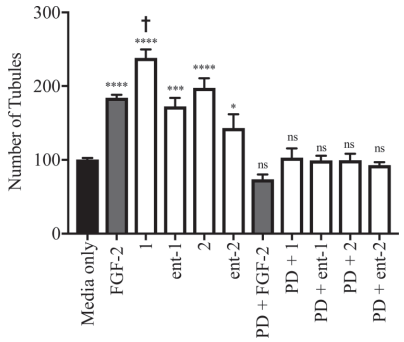

Figure 2. Effect of neolignans **1**, *ent*-**1**, **2**, and *ent*-**2** on tubule formation by human microvascular endothelial cells (HMECs) on reconstituted basement membrane matrix (Matrigel) over a 4 h period compared with that of media (only) and fibroblast growth factor (FGF)-2 (positive) controls as well as when coadministered with the MEK1/2 inhibitor PD (PD98059). The columns represent the mean of the means of 4 independent experiments with each condition performed in triplicate. Error bars represent the standard error of the mean. Statistical significance was determined by one-way ANOVA and Dunnett's multiple comparisons test (compared with media only, i.e., MCDB131 medium with supplements and 0.2% fetal bovine serum (FBS)) using GraphPad Prism software, where **** denotes $P < 0.0001$, *** denotes $P < 0.001$, * denotes $P < 0.05$, ns denotes not significant, and † denotes significance at $P < 0.01$ between FGF-2 and compound **1**. There was no significant difference between FGF-2 and compounds **2**, *ent*-**1**, or *ent*-**2**.

respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on a Fourier transform infrared spectrometer. Samples were analyzed as thin films on KBr plates or as neat material. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, whereas high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution electron ionization (EI) mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[19] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[20] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *(E)-2-Methoxy-1-(methoxymethoxy)-4-(3-(methoxymethoxy)prop-1-en-1-yl)-benzene (4). Step i*: Using a procedure analogous to that described by Bazin et al.,[21] a magnetically stirred solution of ferulic acid (**3**) (30.2 g, 155.5 mmol) in dry methanol (200 mL) was treated with five drops of concentrated sulfuric acid, and the resulting mixture was heated under reflux for 24 h. The solution was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue thus obtained was dissolved in dichloromethane, and the resulting solution was washed with $NaHCO_3$ (2 × 100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this oil to flash chromatography [silica, petroleum ether → 1:5 v/v ethyl acetate/petroleum ether gradient elution] and concentration of the relevant fractions (R_f = 0.6 in 1:1 v/v ethyl acetate/petroleum ether) under reduced pressure afforded ferulic acid methyl ester[22] (30.0 g, 93%) as a white, crystalline solid, mp = 60.9−62.1 °C (lit.[22] mp = 65 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 15.9 Hz, 1H), 7.07 (dd, J = 8.2 and 1.9 Hz, 1H), 7.02 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.29 (d, J = 15.9 Hz, 1H), 5.90 (m, 1H), 3.92 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 148.1, 146.9, 145.1, 127.1, 123.2, 115.3, 114.9, 109.5, 56.1, 51.7. These spectral data matched those reported by Li et al.[22]

Step ii: Chloromethyl methyl ether (MOM-Cl) (12.0 mL, 158.3 mmol) was added dropwise to a magnetically stirred solution of ferulic acid methyl ester (22.0 g, 105.6 mmol) and Hünig's base (i-Pr_2NEt) (27.6 mL, 158.3 mmol) in dry dichloromethane (100 mL) maintained at 0 °C. The resulting mixture was allowed to warm to 22 °C and stirred at this temperature for 14 h whilst being maintained under nitrogen then quenched with NH_4Cl (50 mL of a saturated aqueous solution). The mixture thus obtained was stirred at 22 °C for a further 1 h then treated with $NaHCO_3$ (100 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic phases were washed with Na_2CO_3 (3 × 50 mL of a saturated aqueous solution) and brine (3 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. This oil was subjected to flash chromatography [silica, dichloromethane → 1:20 v/v Et_2O/dichloromethane gradient elution], and concentration of the relevant fractions (R_f = 0.8 in 1:9 v/v Et_2O/dichloromethane) under reduced pressure afforded methyl (*E*)-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate[23] (25.0 g, 94%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 16.0 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.07 (m, 2H), 6.33 (d, J = 16.0 Hz, 1H), 5.26 (s, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 149.9, 148.6, 144.8, 128.8, 122.4, 116.2, 115.9, 110.4, 95.3, 56.5, 56.1, 51.8. These spectral data matched those reported by Lui et al.[23]

Step iii: Aluminum trichloride (14.45 g, 109.2 mmol) was added to dry THF (160 mL), and the resulting suspension was stirred at 0 °C under nitrogen for 0.25 h. $LiAlH_4$ (150 mL of a 1 M solution in THF, 150 mmol) was then added dropwise over 0.5 h, and the resulting suspension was stirred for a further 0.5 h at 0 °C. A solution of methyl (*E*)-3-(3-methoxy-4-

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(methoxymethoxy)phenyl)acrylate (24.97 g, 99.0 mmol) in dry THF (20 mL) was then added (dropwise over 0.5 h) to the reaction mixture that was then stirred at 0 °C for 0.5 h before being allowed to warm to 22 °C and stirred for an additional 1 h at this temperature. The reaction mixture was then cooled to 0 °C, water (5.7 mL) was added dropwise (Caution: hydrogen gas evolution), and stirring then continued for 0.25 h. After this time, NaOH (5.7 mL of a 15% w/v aqueous solution) was added to the reaction mixture, and stirring continued for an additional 0.25 h before more water (17.1 mL) was added. The resulting mixture was warmed to 22 °C, diluted with Et_2O (10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, petroleum ether → ethyl acetate gradient elution) and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/petroleum ether) under reduced pressure afforded (*E*)-3-(3-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol[24] (21.21 g, 96%) as a white, crystalline solid, mp = 51.2−52.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.90 (dd, J = 8.3 and 2.0 Hz, 1H), 6.55 (d, J = 15.9 Hz, 1H), 6.26 (dt, J = 15.9 and 5.9 Hz, 1H), 5.23 (s, 2H), 4.31 (dd, J = 5.9 and 1.5 Hz, 2H), 3.89 (s, 3H), 3.51 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 146.4, 131.4, 131.1, 127.2, 119.7, 116.3, 109.5, 95.5, 63.9, 56.4, 56.0; IR ν_{max} 3399, 2935, 1512, 1464, 1417, 1263, 1154, 1132, 1077, 993, 969 cm^{-1}; MS (ESI, +ve) m/z 247 (100) $[M + Na]^+$; HRMS calcd for $C_{12}H_{16}NaO_4$ $[M + Na]^+$: 247.0946, found: 219.0946.

Step iv: MOM-Cl (10.7 mL, 141.3 mmol) was added dropwise to a magnetically stirred solution of (*E*)-3-(3-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol (21.18 g, 94.2 mmol) and Hünig's base (24.6 mL, 141.3 mmol) in dry dichloromethane (94 mL) maintained at 0 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to 22 °C and stirred at this temperature for 14 h before being quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The mixture thus obtained was stirred for a further 1 h, then the organic layer was separated and washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution). The combined aqueous layers were extracted with ethyl acetate (3 × 100 mL), and then the combined organic phases were washed with NH_4Cl (3 × 50 mL of a saturated aqueous solution), water (1 × 50 mL), and brine (3 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil. This oil was subjected to flash chromatography (silica, dichloromethane → 1:20 v/v Et_2O/dichloromethane gradient elution), and concentration of the relevant fractions (R_f = 0.7 in 1:20 v/v Et_2O/dichloromethane) under reduced pressure afforded compound **4** (25.0 g, 94%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.91 (dd, J = 8.2 and 1.8 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H), 6.18 (dt, J = 15.9 and 6.2 Hz, 1H), 5.23 (s, 2H), 4.70 (s, 2H), 4.22 (d, J = 6.2 Hz, 1H), 3.89 (s, 3H), 3.51 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 146.4, 132.6, 131.4, 124.2, 119.8, 116.3, 109.5, 95.7, 95.5, 68.0, 56.4, 56.0, 55.5; IR ν_{max} 3375, 2934, 1512, 1464, 1265, 1152, 1133, 1102, 1078, 1036, 995, 920 cm^{-1}; MS (ESI, +ve) m/z 291 (100) $[M + Na]^+$, 160 (85); HRMS calcd for $C_{14}H_{20}NaO_5$ $[M + Na]^+$: 219.1208, found: 219.1208.

*(1R,2R)-1-(3-Methoxy-4-(methoxymethoxy)phenyl)-3-(methoxymethoxy)propane-1,2-diol (**5**).* $MeSO_2NH_2$ (856 mg, 9.0 mmol) was added to a magnetically stirred solution of AD-mix-α (12.48 g) in *t*-butanol/water (120 mL of a 1:1 v/v mixture) maintained at 22 °C, and the resulting suspension was stirred for 0.5 h after which time both phases had become clear. This mixture was then cooled to 0 °C before being treated with a solution of alkene **4** (2.00 g, 7.8 mmol) in *t*-butanol (2 mL). The reaction mixture thus obtained was stirred vigorously at 0 °C for 72 h, quenched with Na_2SO_3 (1.0 g), then allowed to warm to 22 °C and stirred at this temperature 12 h. The resulting solution was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography [silica, 1:1 v/v ethyl acetate/petroleum ether → ethyl acetate gradient elution]. Concentration of the relevant fractions (R_f = 0.4 in ethyl acetate) under reduced pressure afforded compound **5** (1.85 g, 78%) as a clear, colorless gum, $[\alpha]^{25}_D$ = +10.7 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 1.9 Hz, 1H), 6.87 (dd, J = 8.2 and 1.9 Hz, 1H), 5.22 (s, 2H), 4.64 (m, 3H), 3.89 (s, 3H), 3.80 (m, 1H), 3.57 (dd, J = 10.7 and 3.3 Hz, 1H), 3.52 (dd, J = 10.7 and 5.5 Hz, 1H), 3.51 (s, 3H), 3.39 (s, 3H), 3.08 (broad d, J = 5.4 Hz, 1H), 3.00 (br d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.4, 134.8, 119.4, 116.4, 110.3, 97.5, 95.6, 75.0, 74.7, 70.1, 56.4, 56.1, 55.8; IR ν_{max} 3435, 2937, 1594, 1513, 1265, 1153, 1034, 989, 920 cm^{-1}; MS (ESI, +ve) m/z 325 (100) $[M + Na]^+$; HRMS calcd for $C_{14}H_{22}NaO_7$ $[M + Na]^+$: 325.1263, found: 325.1259.

*(R)-2-Hydroxy-1-(3-methoxy-4-(methoxymethoxy)-phenyl)-3-(methoxymethoxy)propan-1-one (**6**).* DDQ (2.78 g, 12.25 mmol) was added to a magnetically stirred solution of diol **5** (1.79 g, 5.92 mmol) in dry benzene (30 mL) maintained under nitrogen at 22 °C. The resulting suspension was sonicated for 5 h during which time the temperature of the water in the sonication bath was maintained between 22 and 30 °C through the addition of ice. The reaction mixture thus obtained was cooled then filtered, and the filtrate was concentrated reduced pressure. The residue thus obtained was triturated with cold dichloromethane (4 × 10 mL), and the combined washings were filtered and the filtrate again concentrated under reduced pressure to afford a black oil. Subjection of this material to flash chromatography [silica, dichloromethane → 3:7 v/v Et_2O/dichloromethane gradient elution] and concentration of the relevant fractions (R_f = 0.5 in 3:7 v/v Et_2O/dichloromethane) under reduced pressure afforded compound **6** (1.53 g, 86%) as a clear, pale-yellow oil, $[\alpha]^{25}_D$ = −20.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.0 Hz, 1H), 7.51 (dd, J = 8.4 and 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 5.32 (s, 2H), 5.19 (ddd—simplifies to a dd upon addition of D_2O, J = 7.4, 4.5, and 3.1 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H), 3.99 (d—disappears upon addition of D_2O, J = 6.8 Hz, 1H), 3.95 (s, 3H), 3.92 (dd, J = 10.8 and 3.1 Hz, 1H), 3.85 (dd, J = 10.8 and 4.5 Hz, 1H), 3.52 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 151.8, 150.0, 128.0, 123.1, 114.7, 111.4, 96.9, 95.2, 73.2, 71.1, 56.7, 56.3, 55.5; IR ν_{max} 3444, 2937, 1676, 1595, 1512, 1464, 1266, 1148, 1115, 1080, 1032, 980, 920 cm^{-1}; MS (ESI, +ve) m/z 323 (100) $[M + Na]^+$; HRMS calcd for $C_{14}H_{20}NaO_7$ $[M + Na]^+$: 323.1107, found: 323.1107.

*(R)-1-(3-Methoxy-4-(methoxymethoxy)phenyl)-3-(methoxymethoxy)-1-oxopropan-2-yl 4-Methylbenzenesulfonate (**7**).* A magnetically stirred solution of alcohol **6** (1.52 g 5.06 mmol) in dry dichloromethane (20 mL) maintained under nitrogen was cooled to 0 °C then treated with pyridine (600 μL, 7.59 mmol) and *p*-toluenesulfonic acid anhydride (2.48 g,

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7.6 mmol). The ensuing mixture was allowed to stir at 0 °C for 0.5 h then warmed to 22 °C and stirred at this temperature for an additional 1 h before being re-cooled to 0 °C, quenched with pH 7 buffer (2 mL of a 1 M aqueous solution), then allowed to warm to 22 °C. The mixture thus obtained was diluted with ethyl acetate (50 mL) before being washed with NH_4Cl (1 × 40 mL) and brine (1 × 10 mL) The separated aqueous phase was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (3 × 20 mL) before being dried ($MgSO_4$), filtered, then concentrated under reduced pressure to afford an orange oil. This oil was subjected to flash chromatography (silica, dichloromethane → 1:9 v/v Et_2O/dichloromethane gradient elution) and concentration of the relevant fractions (R_f = 0.6 in 1:9 v/v Et_2O/dichloromethane) under reduced pressure afforded ester **7** (2.14 g, 93%) as a white, crystalline solid, mp = 93.5−95.8 °C, $[\alpha]^{25}_D$ = −34 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.53 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 5.82 (t, *J* = 4.9 Hz, 1H), 5.32 (s, 2H), 4.54 (m, 2H), 3.93 (d, *J* = 4.9 Hz, 2H), 3.91 (s, 3H), 3.52 (s, 3H), 3.25 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 151.7, 149.8, 145.2, 133.5, 129.8, 128.7, 128.2, 123.5, 114.6, 111.6, 96.7, 95.2, 79.8, 67.4, 56.7, 56.2, 55.6, 21.8; IR ν_{max} 3374, 2940, 1690, 1595, 1512, 1464, 1421, 1364, 1267, 1176, 1079, 1030, 976, 923, 814, 666 cm^{-1}; MS (ESI, +ve) *m/z* 477 (100) $[M + Na]^+$; HRMS calcd for $C_{21}H_{26}NaO_9S$ $[M + Na]^+$: 477.1195, found: 477.1194.

*(E)-3-(3-Methoxy-4-((1-(3-methoxy-4-(methoxymethoxy)-phenyl)-3-(methoxymethoxy)-1-oxopropan-2-yl)oxy)-phenyl)acrylaldehyde (**9**).* Cesium carbonate (1.09 g, 3.34 mmol) was added to a solution of 18-crown-6 (874 mg, 3.31 mmol) and coniferaldehyde (**8**) (590 mg, 3.31 mmol) in dry acetonitrile (9 mL) maintained under nitrogen at 22 °C. The resulting suspension was sonicated for 0.5 h, then the supernatant liquid was taken up in a syringe and added dropwise, over 0.25 h, to a magnetically solution of tosylate **7** (990 mg, 2.17 mmol) in dry acetonitrile (20 mL) maintained under nitrogen at 0 °C. The resulting solution was stirred at 0 °C for 5 h then quenched with pH 7 buffer (2 mL of a 1 M aqueous solution) before being allowed to warm to 22 °C. The ensuing mixture was diluted with ethyl acetate (20 mL), and the separated aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography [silica, dichloromethane → 3:7 v/v Et_2O/dichloromethane gradient elution], and concentration of the relevant fractions (R_f = 0.2 in 1:9 v/v Et_2O/dichloromethane) under reduced pressure afforded aryl ether **9** (470 mg, 47%) as a clear, pale-yellow oil, $[\alpha]^{25}_D$ = 0 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 7.7 Hz, 1H), 7.74 (dd, *J* = 8.5 and 1.1 Hz, 1H), 7.66 (s, 1H), 7.35 (d, *J* = 15.8 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.05 (s, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.56 (dd, *J* = 15.8 and 7.7 Hz, 1H), 5.62 (m, 1H), 5.30 (s, 2H), 4.69 (s, 2H), 4.19−4.07 (complex m, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.50 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 193.6, 152.6, 151.6, 150.2, 150.0, 149.8, 129.0, 128.5, 127.3, 123.4, 123.1, 115.5, 114.6, 111.7, 111.2, 96.9, 95.1, 81.7, 68.1, 56.7, 56.1(1), 56.0(7), 55.6; IR ν_{max} 3369, 2932, 1671, 1595, 1509, 1268, 1141, 1127, 1079, 1032, 975, 804 cm^{-1}; MS (ESI, +ve) *m/z* 484 (100) $[M + Na]^+$; HRMS calcd for $C_{24}H_{28}NaO_9$ $[M + Na]^+$: 483.1631, found: 483.1632.

*(E)-3-(4-((3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-oxopropan-2-yl)oxy)-3-met-hoxyphenyl)acrylaldehyde (**10**).* A magnetically stirred solution of aryl ether **9** (465 mg, 1.02 mmol) in dry isopropanol (30 mL) was treated with concentrated hydrochloric acid (3 drops), and the resulting solution was heated at 60 °C for 22 h. The cooled reaction mixture was quenched with $NaHCO_3$ (20 mL of a saturated solution) then diluted with ethyl acetate (60 mL) before being washed with $NaHCO_3$ (2 × 20 mL). The separated aqueous phases were extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (3 × 20 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. This oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/petroleum ether → ethyl acetate gradient elution), and concentration of the relevant fractions (R_f = 0.2 in 3:1 v/v ethyl acetate /petroleum ether) under reduced pressure afforded alcohol **10** (291 mg, 76%) as a pale-yellow foam, $[\alpha]^{25}_D$ = 0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 7.7 Hz, 1H), 7.70 (dd, *J* = 8.4 and 1.9 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 7.04 (dd, *J* = 8.3 and 2.0 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.55 (dd, *J* = 15.9 and 7.7 Hz, 1H), 6.17 (broad s, 1H), 5.55 (m, 1H), 4.13 (m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 2.79 (broad t, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 193.6, 152.4, 151.5, 150.5, 149.7, 147.1, 129.1, 127.6(2), 127.5(7), 124.2, 123.1, 116.7, 114.3, 111.2, 110.7, 83.4, 63.9, 56.3, 56.1; IR ν_{max} 3356, 2938, 1668, 1620, 1591, 1509, 1426, 1270, 1137, 1030, 734 cm^{-1}; MS (ESI, +ve) *m/z* 395 (100) $[M + Na]^+$; HRMS calcd for $C_{20}H_{20}NaO_7$ $[M + Na]^+$: 395.1107, found: 395.1110.

*Compounds (±)-**1** and (±)-**2**.* Polymer-supported borohydride (2.5 mmol g^{-1} on Amberlite A-26, 400 mg, 1.0 mmol) was added in one portion to a magnetically stirred solution of compound **10** (77 mg, 0.21 mmol) in methanol (5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was stirred at this temperature for 4 h then allowed to warm to 22 °C before being filtered, and the solids thus retained were washed with acetic acid in methanol (3 × 10 mL of a 1:99 v/v mixture). The combined filtrates were concentrated under reduced pressure to give a ca. 7:1 mixture of the title compounds (68 mg, 87%) as a light-yellow oil. Subjection of this material to preparative, reverse phase HPLC (Gemini C18 5μ 150 × 21.20 mm^2 column, 25:74.95:0.05 v/v/v/v methanol/water/acetic acid elution, flow rate 17.0 mL/min) afforded two fractions, A and B.

Concentration of fraction A (t_R = 12.0 min) afforded compound (±)-**2**[4e,10] (9 mg, 12%) as a white powder. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 7.11 (d, *J* = 1.9 Hz, 1H), 7.06 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.90−6.85 (complex m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.52 (dt, *J* = 15.8 and 1.7 Hz, 1H), 6.28 (dt, *J* = 15.8 and 5.3 Hz, 2H), 4.89 (d, *J* = 5.3 Hz, 1H), 4.30 (m, 1H), 4.19 (dd, *J* = 5.3 and 1.7 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (partially obscured m, 1H), 3.69 (dd, *J* = 11.6 and 4.0 Hz, 1H) (signals due to three hydroxyl group protons not observed); ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 2.0 Hz, 1H), 7.00 (s, 1H), 6.87 (s, 2H), 6.84 (dd, *J* = 8.2 and 2.0 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.51 (dt, *J* = 15.7 and 1.6 Hz, 1H), 6.24 (dt, *J* = 15.7 and 5.7 Hz, 1H), 4.83 (d, *J* = 5.7 Hz, 1H), 4.36 (m, 1H), 4.20 (dd, *J* = 5.7 and 1.6 Hz, 2H), 3.85 (dd, *J* = 12.0 and 5.6 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.76

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(partially obscured d, J = 3.6 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ see Table 1; IR ν_{max} 3369, 2918, 1509, 1266, 1152, 1122, 1029 cm^{-1}; MS (EI, +ve) m/z 376 (15) ($M^{+\bullet}$), 358 (50), 328 (45), 206 (100); HRMS calcd for $C_{20}H_{24}O_7$ ($M^{+\bullet}$): 376.1522, found: 376.1524.

Concentration of fraction B (t_R = 13.2 min) afforded compound (±)-**1**[41,10] (57 mg, 73%) as a white powder. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 7.11 (d, J = 8.4 Hz, 1H), 7.10−7.09 (complex m, 2H), 6.91 (dd, J = 8.4 and 2.1 Hz, 1H), 6.90 (dd, J = 8.1 and 1.9 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.54 (dt, J = 15.9 and 1.7 Hz, 1H), 6.30 (dt, J = 15.9 and 5.3 Hz, 1H), 4.88 (d, J = 6.3 Hz, 1H), 4.20 (m, 3H), 3.90 (s, 3H), 3.81 (s, 3H), 3.68 (dd, J = 11.8 and 3.7 Hz, 1H), 3.50 (dd, J = 11.8 and 5.7 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (s, 1H), 7.03 (s, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 6.25 (dt, J = 15.8 and 5.7 Hz, 1H), 4.90 (partially obscured m, 1H), 4.31 (app. q, J = 5.0 Hz, 1H), 4.20 (d, J = 5.7 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.74 (dd, J = 12.1, 3.7 Hz, 1H), 3.48 (dd, J = 12.0, 5.2 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ see Table 1; IR ν_{max} 3369, 2931, 1604, 1510, 1263, 1129, 1079, 1029, 965 cm^{-1}; MS (ESI, +ve) m/z 399 (100) [M + Na]$^+$; HRMS calcd for $C_{20}H_{24}NaO_7$ [M + Na]$^+$: 399.1420, found: 399.1420.

*2-(4-Allyl-2-methoxyphenoxy)acetic Acid (**14**).* Compound **14** was prepared in 85% overall yield from ethyl α-bromoacetate and eugenol (**13**) following a protocol reported by Spurg and Waldvogel[25] to give a white, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, J = 7.9 Hz, 1H), 6.76 (m, 2H), 5.94 (m, 1H), 5.11 (m, 1H), 5.08 (m, 1H), 4.63 (s, 2H), 3.90 (s, 3H), 3.36 (d, J = 6.7 Hz, 2H) (signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 149.9, 145.7, 137.2, 136.5, 121.3, 117.6, 116.3, 112.7, 69.0, 56.1, 40.0. These spectral data matched those reported by Labarrios and co-workers.[26]

*(S)-3-(2-(4-Allyl-2-methoxyphenoxy)acetyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**15**).* Oxalyl chloride (710 μL, 8.14 mmol) was added dropwise over 0.08 h to a magnetically stirred solution of carboxylic acid **14** (1.65 g, 7.40 mmol) and dimethylformamide (DMF) (28 μL, 0.37 mmol) in dichloromethane (15 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 22 °C and stirred until gas evolution ceased (ca. 1 h). The dichloromethane was then removed by sparging the reaction mixture with a stream of nitrogen followed by further concentration of the reaction mixture under reduced pressure. The acid chloride thus obtained was dissolved in dry THF (15 mL). In a separate flask, *n*-BuLi (4.52 mL of a 1.5 M solution in hexanes, 6.79 mmol) was added dropwise over 0.25 h to a magnetically stirred solution of (*S*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**12**)[14b] (1.74 g, 6.17 mmol) in dry THF (150 mL) maintained at 0 °C. The resulting solution was stirred at this temperature for 0.5 h then cooled to −78 °C. The previously formed solution of the acid chloride in THF was then added dropwise over 0.25 h, and stirring of the combined solutions continued at −78 °C for 0.5 h. The cooling bath was then removed, and the reaction mixture was allowed to warm to 22 °C and stirring was continued for 3 h. After this time, the reaction mixture was cooled to 0 °C and quenched with NH_4Cl (30 mL of a saturated aqueous solution) then acetic acid (5 mL). The ensuing mixture was allowed to warm, over 0.25 h, to 22 °C then it was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) and brine (2 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing viscous, clear, and light-yellow oil was subjected to flash column chromatography (silica, hexane → 1:4 v/v ethyl acetate/hexane gradient elution), and concentration of the appropriate fractions (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded amide **15** (2.79 g, 93%) as a white foam, $[\alpha]^{20}_D$ = −156 (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.27 (complex m, 10H), 6.70 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 8.2 and 2.0 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 5.94 (m, 1H), 5.37 (d, J = 3.3 Hz, 1H), 5.24 (d, J = 17.7 Hz, 1H), 5.12−5.01 (complex m, 3H), 3.82 (s, 3H), 3.31 (d, J = 6.8 Hz, 2H), 2.00 (m, 1H), 0.90 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 153.2, 149.4, 145.6, 142.1, 137.9, 137.7, 134.1, 129.2, 129.0, 128.6, 128.3, 126.0, 125.8, 120.4, 115.8, 113.6, 112.6, 91.1, 68.1, 64.9, 56.0, 40.0, 30.0, 21.9, 16.6; IR ν_{max} 2969, 1780, 1724, 1510, 1257, 1209, 1178, 1147, 1035, 992, 733, 701 cm^{-1}; MS (ESI, +ve) m/z 508 (100) [M + Na]$^+$; HRMS calcd for $C_{30}H_{31}NNaO_5$ [M + Na]$^+$: 508.2100, found: 508.2099.

*(R)-3-(2-(4-Allyl-2-methoxyphenoxy)acetyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (ent-**15**).* Compound *ent*-**15** was prepared in an analogous fashion to that described immediately above from compounds *ent*-**12** and **14**. Flash chromatographic purification then gave oxazolidin-2-one *ent*-**15** (8.79 g, quantitative yield) as a white foam, $[\alpha]^{20}_D$ = +160 (c = 0.3, $CHCl_3$). All the other spectral data acquired on this material were identical with those detailed above for compound **15**.

*(1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphe-nyl)propane-1,3-diol (**17**).* *Step i*: A magnetically stirred solution of amide **15** (2.00 g, 4.12 mmol) in dry dichloromethane (8 mL) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 0.08 h, with freshly prepared[14b] Bu_2BOTf (1.07 mL, 1.35 g, 4.94 mmol). The ensuing mixture was allowed to warm to 22 °C, stirred at this temperature for 0.25 h, then freshly distilled Hünig's base (970 μL, 5.56 mmol) was added dropwise over 0.08 h. Stirring was continued at 22 °C for another 0.5 h then the reaction mixture was cooled to −78 °C before a solution of aldehyde **16**[27] (1.35 g, 4.94 mmol) in dichloromethane (4 mL) was added via syringe pump over 0.75 h. The ensuing mixture was stirred at −78 °C for a further 1 h then warmed to 0 °C, stirred at this temperature for 4 h, then quenched with phosphate buffer (15 mL of a 1 M aqueous solution at pH 7) before being treated with methanol/30% aq. hydrogen peroxide (10 mL of a 1:1 v/v mixture) and allowed to warm to 22 °C over 1 h. The biphasic mixture thus obtained was diluted with water (20 mL), and the separated aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing thick oil was subjected to flash column chromatography (silica, dichloromethane → 1:19 v/v Et_2O/dichloromethane gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 1:19 v/v Et_2O/dichloromethane) afforded the anticipated aldol product (2.58 g, 83%) as a white foam, $[\alpha]^{20}_D$ = −78.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (complex m, 10H), 6.87 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H),

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6.63 (dd, J = 8.1 and 2.0 Hz, 1H), 6.57 (dd, J = 8.1 and 2.0 Hz, 1H), 6.48 (d, J = 8.1 Hz, 1H), 6.10 (m, 1H), 5.89 (m, 1H), 5.35 (d, J = 2.9 Hz, 1H), 5.05 (m 1H), 5.01 (m, 1H), 4.67 (t, J = 5.0 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.28 (m, 3H), 1.95 (m, 1H), 0.98 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.68 (d, J = 6.7 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 152.9, 150.7, 150.4, 145.5, 144.7, 141.6, 138.1, 137.5, 135.6, 131.9, 129.0(3), 129.0(0), 128.5, 128.1, 125.9, 125.4, 120.8, 120.5, 119.3, 118.5, 115.9, 113.1, 110.6, 90.1, 81.4, 74.0, 65.1, 56.0, 55.3, 40.0, 30.1, 25.9, 21.8, 18.6, 16.3, −4.5, −4.6; IR ν_{max} 3452, 2954, 2930, 2858, 1777, 1716, 1510, 1450, 1369, 1283, 1210, 1153, 1035, 908, 702 cm^{-1}; MS (ESI, +ve) m/z 774 (100) $[M + Na]^+$; HRMS calcd for $C_{44}H_{53}NNaO_8Si$ $[M + Na]^+$: 774.3438, found: 774.3433.

Step ii: Methanol (230 μL, 5.65 mmol) was added to a magnetically stirred solution of the above-mentioned aldol product (1.70 g, 2.26 mmol) in THF (25 mL) maintained under nitrogen at 22 °C. The resulting solution was cooled to 0 °C, and lithium borohydride (123 mg, 5.65 mmol) was then added in portions over 0.08 h. The ensuing mixture was stirred at 0 °C for 0.5 h then warmed to 22 °C and stirred at this temperature for 2 h before being quenched with NH_4Cl (20 mL of a saturated aqueous solution) then diluted with Et_2O (100 mL). The separated aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic extracts were washed with brine (2 × 20 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1:19 v/v Et_2O/dichloromethane → 1:4 v/v Et_2O/dichloromethane gradient elution), and concentration of the appropriate fractions (R_f = 0.4 in 1:4 v/v Et_2O/dichloromethane) afforded diol **17** (982 mg, 92%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −63.3 (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 6.88 (dd, J = 8.1 and 1.9 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 1.9 Hz, 1H), 6.74 (dd, J = 8.0 and 1.9 Hz, 1H), 5.95 (m, 1H), 5.11 (m, 1H), 5.07 (t, J = 1.4 Hz, 1H), 4.95 (d, J = 8.0 Hz, 1H), 3.97 (dt, J = 7.6 and 3.6 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.60 (dd, J = 12.5 and 3.2 Hz, 1H), 3.47 (dd, J = 12.5 and 4.0 Hz, 1H), 3.35 (d, J = 6.8 Hz, 2H), 0.99 (s, 9H), 0.14 (s, 6H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 151.2, 146.0, 145.1, 137.3, 136.5, 133.2, 121.7, 121.2, 119.8, 116.2, 112.6, 110.8, 90.0, 74.2, 61.3, 56.0, 55.6, 40.1, 25.9, 18.6, −4.5(0), −4.5(2) (one signal obscured or overlapping); IR ν_{max} 3453, 2954, 2931, 2857, 1510, 1465, 1419, 1283, 1264, 1228, 1156, 1034, 911, 840, 782 cm^{-1}; MS (ESI, +ve) m/z (%) 497 (100) $[M + Na]^+$; HRMS calcd for $C_{26}H_{38}NaO_6Si$ $[M + Na]^+$: 497.2335, found: 497.2332.

(1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-1-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphen-yl)propane-1,3-diol (ent-17). Diol *ent*-**17** was prepared as described immediately above from precursor *ent*-**15** and aldehyde **16**. Flash chromatographic purification of the product from step i gave the expected aldol product (2.15 g, 69%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +77.7 (c = 1, $CHCl_3$). All the other spectral data acquired on this material were identical with those reported above for the product from step i. The conditions defined in step ii above were employed to produce diol *ent*-**17** (684 mg, 96%), which was obtained as a clear, colorless oil, $[\alpha]^{20}_D$ = +66.2 (c = 0.7, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **17**.

(E)-3-(4-(((1R,2R)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)-1,3-dihydroxypr-oxypropan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (18). Acetic acid (370 μL, 6.5 mmol), sodium acetate (6.5 mg, 0.08 mmol), molecular sieves (2 mg of activated 4 Å material), 4,5-DAF (5.1 mg, 7 mol %), and $Pd(OAc)_2$ (6.3 mg, 7 mol %) were added sequentially to a magnetically stirred solution of compound **17** (190 mg, 0.40 mmol) in 1,4-dioxane (2.4 mL) maintained at 22 °C. Oxygen from a balloon was bubbled through the resulting solution for 0.25 h, which was then heated to 60 °C and maintained under an atmosphere of oxygen. After 48 h, the reaction mixture was cooled to 22 °C, and the solvent was removed under reduced pressure. The black residue thus obtained was subjected to flash column chromatography (silica, hexane → 3:2 v/v ethyl acetate/hexane gradient elution), and concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v EtOAc/hexane) afforded acetate **18** (103 mg, 48%) as a pale-yellow oil, $[\alpha]^{20}_D$ = −69.1 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 1H), 7.01−6.92 (complex m, 3H), 6.87 (dd, J = 8.0 and 1.9 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.21 (dt, J = 15.9 and 6.5 Hz, 1H), 4.95 (dd, J = 7.9 and 2.0 Hz, 1H), 4.72 (dd, J = 6.5 and 1.3 Hz, 2H), 4.03 (m, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.61 (m, 1H), 3.55−3.46 (complex m, 2H), 2.57 (m, 1H), 2.11 (s, 3H), 0.99 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.4, 151.3, 147.9, 145.2, 133.8, 133.1, 132.6, 122.9, 121.0, 120.9, 120.5, 119.7, 110.8, 110.0, 89.7, 74.2, 65.1, 61.4, 56.1, 55.7, 25.9, 21.2, 18.6, −4.5(0), −4.5(2); IR ν_{max} 3467, 2952, 2933, 2857, 1739, 1510, 1465, 1419, 1251, 1232, 1158, 1128, 1030, 908, 840 cm^{-1}; MS (ESI, +ve) m/z 555 (100) $[M + Na]^+$; HRMS calcd for $C_{28}H_{40}NaO_8Si$ $[M + Na]^+$: 555.2390, found: 555.2390.

(E)-3-(4-(((1S,2S)-1-(4-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)-1,3-dihydroxypro-pan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (ent-18). Allylic oxidation of compound *ent*-**17** in the same manner as that described above for congener **17** afforded, after flash chromatographic purification, compound *ent*-**18** (71 mg, 65%) as a pale-yellow oil, $[\alpha]^{20}_D$ = +47.5 (c = 1.6, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **18**.

(1R,2R)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methox-yphenoxy)propane-1,3-diol (ent-1). K_2CO_3 (270 mg, 1.95 mmol) was added to a magnetically stirred solution of acetate **18** (45 mg, 0.085 mmol) in methanol (5 mL) containing water (100 μL) and maintained at 22 °C under a nitrogen atmosphere. The ensuing mixture was stirred at this temperature for 18 h then diluted with ethyl acetate (20 mL), acidified (to pH 5) using acetic acid (ca. 200 μL), then washed with water (1 × 5 mL) and brine (2 × 5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash column chromatography (silica, 1:19 v/v methanol/dichloromethane → 1:9 v/v methanol/dichloromethane gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 1:19 v/v methanol/dichloromethane) afforded compound *ent*-**1** (25 mg, 79%) as a clear, colorless gum, $[\alpha]^{20}_D$ = −36.7 (c = 0.9, methanol). ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 (s, 1H), 7.03 (s, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.75 (dd, J = 8.2 and 1.4 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.26 (dt, J = 16.0 and 5.4 Hz, 1H), 4.88 (m, 1H), 4.29 (m, 1H), 4.20 (d, J = 5.7 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.73 (dd, J = 11.9 and

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4.0 Hz, 1H), 3.47 (dd, J = 11.9 and 5.4 Hz, 1H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 151.8, 149.2, 148.8, 147.2, 133.8, 133.1, 131.4, 128.6, 120.8, 120.7, 118.8, 115.8, 111.7, 111.3, 87.1, 74.0, 63.8, 61.9, 56.5, 56.3; IR ν_{max} 3348, 2934, 1602, 1509, 1464, 1263, 1226, 1156, 1130, 1027, 968 cm^{-1}; MS (ESI, +ve) m/z 399 (100) $[M + Na]^+$; HRMS calcd for $C_{20}H_{24}NaO_7$ $[M + Na]^+$: 399.1420, found: 399.1419; HPLC analysis: Trefoil CEL1 column, 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature 40 °C, detection at λ = 254 nm, t_{major} = 6.03 min, ee > 99%.

*(1S,2S)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methoxy-phenoxy)propane-1,3-diol (**1**).* Treatment of acetate *ent*-**18** with potassium carbonate in the same manner as that described above gave neolignan **1** (28 mg, 93%) as a clear, colorless gum, $[\alpha]^{20}_D$ = +32.4 (c = 0.2, methanol). All other spectral data acquired on this material were identical with those reported above for compound *ent*-**1**. HPLC analysis: Trefoil CEL1 column, 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature 40 °C, detection at λ = 254 nm, t_{minor} = 5.86 min, t_{major} = 6.05 min, ee = 90%.

*4-((1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxyprop-yl)-2-methoxyphenol (**19**).* The following one-pot procedure for preparing compound **19** was established after that used to prepare its enantiomer (*ent*-**19**) and proved to be the more efficient one. Thus, a magnetically stirred solution of diol **17** (565 mg, 1.19 mmol) in DMF (4 mL) was cooled to 0 °C and treated sequentially with imidazole (162 mg, 2.38 mmol) and TBDMS-Cl (194 mg, 1.25 mmol). The ice bath was then removed, and the resulting solution was stirred at 22 °C for 1.5 h before being treated with Cs_2CO_3 (774 mg, 3.38 mmol) and water (400 μL). The resulting mixture was stirred at 22 °C for 2 h then heated at 40 °C for 4 h. The cooled reaction mixture was stirred at 22 °C for 16 h before being diluted with ethyl acetate (30 mL) and washed with NH_4Cl (3 × 10 mL of a saturated aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 10 mL) and the combined organic phases washed with brine (2 × 10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting pale-yellow residue was subjected to flash column chromatography (silica, 1:9 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.2 in 1:19 v/v Et_2O/dichloromethane) afforded phenol **19** (544 mg, 96%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −103 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.1 Hz, 1H), 6.93 (s, 1H), 6.87 (m, 2H), 6.74 (d, J = 2.0 Hz, 1H), 6.71 (dd, J = 8.1 and 2.0 Hz, 1H), 5.96 (m, 1H), 5.10 (m, 1H), 5.07 (m, 1H), 4.82 (dd, J = 7.7 and 2.6 Hz, 1H), 4.21 (d, J = 2.6 Hz, 1H), 4.03 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.72 (dd, J = 11.2 and 3.4 Hz, 1H), 3.63 (dd, J = 11.2 and 5.4 Hz, 1H), 3.37 (d, J = 6.8 Hz, 2H), 0.88 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H) (signal due to one hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.0, 146.6, 145.5, 137.6, 135.4, 132.4, 121.1, 120.6, 120.3, 116.0, 114.2, 112.4, 109.6, 89.0, 74.0, 62.7, 56.1, 55.9, 40.1, 26.0, 18.5, −5.3(0), −5.3(4); IR ν_{max} 3466, 2954, 2930, 2856, 1606, 1509, 1454, 1266, 1227, 1127, 1035, 836, 779 cm^{-1}; MS (ESI, +ve) m/z (%) = 497 (100) $[M + Na]^+$; HRMS calcd for $C_{26}H_{38}NaO_6Si$ $[M + Na]^+$: 497.2335, found: 497.2334.

4-((1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropy-l)-2-methoxyphenol (ent-19). A magnetically stirred solution of diol *ent*-**17** (452 mg, 0.95 mmol) in dichloromethane (6 mL) was cooled to −5 °C and treated sequentially with imidazole (129 mg, 1.9 mmol) and TBDMS-Cl (155 mg, 1.00 mmol). The cooling bath was then removed, and the reaction mixture was stirred at 22 °C for 16 h before being quenched with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic phases were then washed with brine (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the anticipated bis-TBDMS ether (386 mg) as a light-yellow oil. This oil was dissolved in DMF (1 mL), and the resulting solution was treated with Cs_2CO_3 (307 mg, 0.95 mmol) and water (100 μL) then stirred at 22 °C for 24 h. After this time, another batch of Cs_2CO_3 (200 mg, 0.62 mmol) was added, and stirring continued for an additional 24 h. The reaction mixture was then diluted with ethyl acetate (30 mL) before being washed with NH_4Cl (3 × 10 mL of a saturated aqueous solution). The combined aqueous washings were extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were then washed with brine (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1:9 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.2 in 1:19 v/v Et_2O /DCM) afforded phenol *ent*-**19** (232 mg, 51% over two steps) as a clear, colorless oil, $[\alpha]^{20}_D$ = +98.8 (c = 0.7, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **19**.

*4-((1R,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxyprop-yl)-2-methoxyphenyl 4-Methylbenzenesulfonate (**20**).* *p*-Toluenesulfonyl chloride (216 mg, 1.13 mmol) was added in one portion to a magnetically stirred solution of phenol **19** (512 mg, 1.08 mmol) and triethylamine (225 μL, 1.62 mmol) in dichloromethane (50 mL) maintained at 0 °C. DMAP (6.6 mg, 0.05 mmol) was then added to the reaction mixture, and stirring was continued at 0 °C for 1 h. The resulting mixture was quenched with NH_4Cl (20 mL of an aqueous solution), and the separated aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with brine (2 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The pale-yellow oil thus obtained was subjected to flash column chromatography (silica, 1:24 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.6 in 1:19 v/v Et_2O/dichloromethane) afforded phenol **20** (590 mg, 87%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −54.2 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94−6.88 (complex m, 2H), 6.73−6.67 (complex m, 2H), 5.95 (m, 1H), 5.12−5.18 (complex m 1H), 5.06 (m, 1H), 4.89 (dd, J = 7.0 and 3.2 Hz, 1H), 4.24 (d, J = 3.2 Hz, 1H), 4.01 (m, 1H), 3.85 (s, 3H), 3.73 (dd, J = 11.2 and 3.8 Hz, 1H), 3.62 (dd, J = 11.2 and 4.9 Hz, 1H), 3.51 (s, 3H), 3.34 (d, J = 6.7 Hz, 2H), 2.42 (s, 3H), 0.89 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.6, 146.4, 144.9, 140.7, 137.8, 137.3, 135.6, 133.2, 129.3, 128.7, 123.6, 121.0, 120.0, 119.3, 115.9, 112.4, 111.3, 87.8, 73.4, 62.3, 55.7, 55.5, 39.9, 25.9, 21.7, 18.3, −5.5 (one signal obscured or overlapping); IR ν_{max} 3475, 2951, 2931, 2856, 1600, 1506, 1464, 1419, 1264, 1176, 1092, 1035, 837, 779 cm^{-1}; MS (ESI, +ve) m/z 651 (100) [M +

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Na]$^+$; HRMS calcd for $C_{33}H_{44}NaO_8SSi$ [M + Na]$^+$: 651.2424, found: 651.2423.

*4-((1S,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-2-methoxyphenyl 4-Methylbenzenesulfonate (ent-**20**).* Treatment of compound *ent*-**19** with *p*-toluenesulfonyl chloride, Et_3N, and DMAP in the same manner as that described immediately above gave ester *ent*-**20** (252 mg, 91%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +58.4 (*c* = 0.8, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **20**.

*(1S,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-(3-methoxy-4-(tosyloxy)phenyl)propyl 4-Nitrobenzoate (**21**).* A magnetically stirred solution of compound **20** (580 mg, 0.92 mmol), triphenylphosphine (290 mg, 1.11 mmol), and *p*-nitrobenzoic acid (185 mg, 1.11 mmol) in dry THF (40 mL) was cooled to −10 °C, and DEAD (180 μL, 1.11 mmol) was then added to the reaction mixture over 0.25 h. The resulting solution was stirred at −10 °C for 0.5 h before being warmed to 22 °C, and stirring then continued for an additional 16 h. The resulting solution was concentrated under reduced pressure, and the light-yellow solid thus obtained was subjected to flash chromatography (silica, hexane → 3:17 v/v ethyl acetate/hexane gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:4 v/ethyl acetate/hexane) afforded *p*-nitrobenzoate **21** (602 mg, 84%) as a white, crystalline solid, mp = 107−108 °C, $[\alpha]^{20}_D$ = −4.3 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 1H), 7.15 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.1 and 2.0 Hz, 1H), 6.25 (d, *J* = 4.4 Hz, 1H), 5.93 (m, 1H), 5.07 (s, 1H), 5.05 (m, 1H), 4.74 (m, 1H), 3.87 (dd, *J* = 10.6 and 5.2 Hz, 1H), 3.75 (s, 3H), 3.62−3.55 (complex m, 4H), 3.32 (d, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 151.7, 150.7, 150.6, 146.4, 145.1, 138.6, 137.5, 135.9, 135.5, 135.1, 133.5, 130.9, 129.5, 128.7, 123.7, 123.6, 120.8(3), 120.7(7), 118.3, 116.0, 113.4, 113.1, 81.7, 76.4, 61.9, 55.9, 55.8, 40.0, 26.0, 21.8, 18.3, −5.2(9), −5.3(4); IR ν_{max} 2930, 2856, 1728, 1602, 1527, 1505, 1464, 1373, 1261, 1177, 1155, 1091, 1034, 835, 813, 780, 750, 717 cm^{-1}; MS (ESI, +ve) *m/z* 800 (100) [M + Na]$^+$; HRMS calcd for $C_{40}H_{47}NNaO_{11}SSi$ [M + Na]$^+$: 800.2537, found: 800.2537.

*(1R,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-(3-methoxy-4-(tosyloxy)phenyl)propyl 4-Nitrobenzoate (ent-**21**).* Treatment of compound *ent*-**20** with *p*-nitrobenzoic acid, Ph_3P, and DEAD in the same manner as that described above gave ester *ent*-**21** (256 mg, 82%) as a white, crystalline solid, $[\alpha]^{20}_D$ = +4.3 (*c* = 1.1, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **21**.

*4-((1S,2R)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-2-methoxyphenyl 4-Methylbenzenesulfonate (**22**).* A magnetically stirred solution of *p*-nitrobenzoate **21** (569 mg, 0.73 mmol) in THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with NaOH (5 mL of a 1 M aqueous solution, 5 mmol). The ensuing mixture was stirred at 0 °C for 0.5 h then warmed to 22 °C, and after 0.5 h, diluted with ethyl acetate (50 mL). The separated organic layer was washed with $NaHCO_3$ (2 × 10 mL), and the combined aqueous washings were extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (2 × 15 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash column chromatography (silica, 1:49 v/v Et_2O/dichloromethane), and concentration of the appropriate fractions (R_f = 0.3 in 1:49 v/v Et_2O/DCM) afforded alcohol **22** (340 mg, 74%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −8.0 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.26 (partially obscured d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 6.72 (m, 2H), 5.95 (m, 1H), 5.10 (m, 1H), 5.06 (s, 1H), 4.92 (t, *J* = 4.7 Hz, 1H), 4.26 (d, *J* = 4.9 Hz, 1H), 4.17 (m, 1H), 3.84 (s, 3H), 3.83 (partially obscured m, 1H), 3.63 (dd, *J* = 11.0 and 5.1 Hz, 1H), 3.52 (s, 3H), 3.34 (d, *J* = 6.8 Hz, 1H), 2.42 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) (signal due to the hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 151.3, 145.6, 145.0, 140.7, 137.7, 137.4, 135.9, 133.4, 129.4, 128.8, 123.7, 121.3, 120.5, 118.9, 116.1, 112.7, 111.2, 85.5, 73.8, 62.6, 56.0, 55.6, 40.1, 26.0, 21.8, 18.3, −5.3, −5.4; IR ν_{max} 3473, 2952, 2930, 2856, 1600, 1505, 1463, 1418, 1373, 1262, 1175, 1117 1090, 1034, 836, 777, 716, 662 cm^{-1}; MS (ESI, +ve) *m/z* 651 (100) [M + Na]$^+$; HRMS calcd for $C_{33}H_{44}NaO_8SSi$ [M + Na]$^+$: 651.2424, found: 651.2424.

*4-((1R,2S)-2-(4-Allyl-2-methoxyphenoxy)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)-2-methoxyphenyl 4-Methylbenzenesulfonate (ent-**22**).* Treatment of ester *ent*-**21** with NaOH in THF in the same manner as that described immediately above gave alcohol *ent*-**22** (171 mg, 83%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +7.5 (*c* = 0.6, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **22**.

*(E)-3-(4-(((1S,2R)-3-((tert-Butyldimethylsilyl)oxy)-1-hydroxy-1-(3-methoxy-4-(tosyloxy)-phenyl)propan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (**23**).* Acetic acid (85 μL, 1.5 mmol), sodium acetate (1.5 mg, 0.02 mmol), molecular sieves (2 mg of activated 4 Å material), 4,5-DAF (1.2 mg, 8 mol %), and $Pd(OAc)_2$ (1.5 mg, 8 mol %) were added, sequentially, to a magnetically stirred solution of alkene **22** (48 mg, 0.076 mmol) in 1,4-dioxane (800 μL) maintained at 22 °C. Oxygen from a balloon was gently bubbled through the reaction mixture for 0.25 h, then the solution was heated at 60 °C with vigorous stirring under an atmosphere of oxygen. After 66 h, the reaction mixture was cooled to 22 °C, and the solvent was removed under reduced pressure. The ensuing black residue was subjected to flash column chromatography (silica, hexane → 3:2 v/v ethyl acetate/hexane gradient elution), and concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded ester **23** (33 mg, 64%) as a clear, colorless oil, $[\alpha]^{20}_D$ = −18.6 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.24 (partially obscured m, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.99 (m, 1H), 6.93 (s, 1H), 6.91−6.87 (complex m, 3H), 6.59 (dt, *J* = 15.8 and 1.1 Hz, 1H), 6.19 (dt, *J* = 15.8 and 6.5 Hz, 1H), 4.93 (t, *J* = 4.8 Hz, 1H), 4.71 (dd, *J* = 6.5 and 1.1 Hz, 2H), 4.23 (m, 1H), 4.10 (d, *J* = 4.8 Hz, 1H), 3.86 (s, 3H), 3.83 (partially obscured m, 1H), 3.68 (m, 1H), 3.53 (s, 3H), 2.42 (s, 3H), 2.10 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.7, 151.3, 147.5, 145.0, 140.6, 137.7, 134.0, 133.3, 131.9, 129.4, 128.8, 123.7, 122.5, 120.2, 119.7, 118.9, 111.2, 110.1, 85.0, 74.0, 65.2, 62.6, 56.0, 55.6, 26.0, 21.8, 21.2, 18.3, −5.3, −5.4; IR ν_{max} 3475, 2932, 2856, 1737, 1600, 1506, 1464, 1418, 1372, 1251, 1229, 1175, 1117, 1091, 1031, 964, 837, 752, 716, 662 cm^{-1}; MS (ESI, +ve) *m/z* 709 (100) [M + Na]$^+$; HRMS calcd for $C_{35}H_{46}NaO_{10}SSi$ [M + Na]$^+$: 709.2479, found: 709.2478.

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*(E)-3-(4-(((1R,2S)-3-((tert-Butyldimethylsilyl)oxy)-1-hydroxy-1-(3-methoxy-4-(tosyloxy)-phenyl)propan-2-yl)oxy)-3-methoxyphenyl)allyl Acetate (ent-**23**).* Oxidation of alkene *ent*-**22** in an analogous fashion to that described immediately above gave acetate *ent*-**23** (67 mg, 33%) as a clear, colorless oil, $[\alpha]^{20}_{D}$ = +17.7 (*c* = 1, $CHCl_3$). All other spectral data acquired on this material were identical with those reported above for compound **23**.

*(1S,2R)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methoxyp-henoxy)propane-1,3-diol (ent-**2**).* TBAF·$x$$H_2O$ (37 mg, ca. 0.12 mmol) was added in one portion to a magnetically stirred solution of acetate **23** (55 mg, 0.080 mmol) in THF (3 mL) maintained at 22 °C under a nitrogen atmosphere. After 1 h, the reaction mixture was treated with methanol (3 mL) then NaOH (1 mL of a 3 M aqueous solution, 3 mmol) before being heated at 80 °C. After 3 h, the reaction mixture was cooled to 22 °C, acidified to pH 5 using acetic acid, then diluted with ethyl acetate (15 mL). The separated organic phase was washed with brine (3 × 5 mL of a ca. 13 wt % solution), and the combined aqueous washings were extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL of a ca. 13 wt % solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow residue was subjected to flash column chromatography (silica, 1:19 v/v methanol/dichloromethane → 1:9 v/v methanol/dichloromethane gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 1:9 v/v methanol/dichloromethane) afforded compound *ent*-**2** (22 mg, 73%) as a clear, colorless gum, $[\alpha]^{20}_{D}$ = −8.2 (*c* = 1.1, methanol). ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 1.9 Hz, 1H), 6.99 (broad s, 1H), 6.88−6.86 (complex m, 2H), 6.84 (dd, *J* = 8.1 and 1.9 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.51 (dt, *J* = 15.9 and 1.5 Hz, 1H), 6.23 (dt, *J* = 15.8 and 5.8 Hz, 1H), 4.83 (d, *J* = 5.8 Hz, 1H), 4.36 (ddd, *J* = 5.8, 5.7 and 3.7 Hz, 1H), 4.19 (dd, *J* = 5.8 and 1.5 Hz, 2H), 3.85 (dd, *J* = 12.0 and 5.7 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 12.0 and 3.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.9, 148.9, 148.7, 147.0, 134.1, 133.0, 131.4, 128.5, 121.0, 120.6, 118.9, 115.6, 111.9, 111.4, 86.2, 74.1, 63.7, 62.2, 56.5, 56.3; IR ν_{max} 3345, 2937, 1602, 1509, 1463, 1264, 1128, 1028, 968 cm^{-1}; MS (ESI, +ve) *m*/*z* 399 (100) $[M + Na]^+$; HRMS calcd for $C_{20}H_{24}NaO_7$ $[M + Na]^+$: 399.1420, found: 399.1419; HPLC analysis: Chiracel AS-H column, 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, detection at λ = 254 nm, *t* = 35.8 min, ee > 99%.

*(1R,2S)-1-(4-Hydroxy-3-methoxyphenyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2-methoxyp-henoxy)propane-1,3-diol (**2**).* Treatment of compound *ent*-**23** with TBAF then aqueous sodium hydroxide in an analogous fashion to that described immediately above gave compound **2**[9k] (6.8 mg, 73%) as a clear, colorless gum, $[\alpha]^{20}_{D}$ = +7.4 (*c* = 0.5, methanol) {lit.[9k] $[\alpha]^{20}_{D}$ = +10.8 (*c* = 1, $CHCl_3$)}. ^{1}H NMR [600 MHz, $(CD_3)_2SO$] δ 8.71 (s, 1H), 6.99 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.83 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.72 (m, 2H), 6.43 (dt, *J* = 15.9 and 1.9 Hz, 1H), 6.22 (dt, *J* = 15.9 and 5.5 Hz, 1H), 5.27 (d, *J* = 4.7 Hz, 1H), 4.75 (app. t, *J* = 5.6 Hz, 1H), 4.70 (app. t, *J* = 4.9 Hz, 1H), 4.56 (app. t, *J* = 5.6 Hz, 1H), 4.29 (m, 1H), 4.08 (m, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.60 (m, 2H); ^{13}C NMR [150 MHz, $(CD_3)_2SO$] δ 149.6, 147.4, 146.8, 145.3, 133.0, 129.9, 128.4, 128.3, 119.3, 118.8, 115.5, 114.4, 111.3, 109.8, 83.6, 71.5, 61.4, 60.0, 55.5, 55.3. These spectral data matched those reported by Nair and co-workers.[9k] All other spectral data acquired on this material were identical with those reported above for compound *ent*-**2**. HPLC analysis: Chiracel AS-H column, 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, detection at λ = 254 nm, *t* = 43.2 min, ee > 99%.

Endothelial Cell Tubule Formation Assay. Human microvascular endothelial cells (HMECs) were grown in MCDB131 media supplemented with 10% fetal bovine serum (FBS), hydrocortisone (500 μg/mL), epidermal growth factor (0.01 mg/mL), L-glutamine (2 mM), and antibiotics. At 80−90% confluency, the cells were trypsinized, pelleted by centrifugation, and resuspended in MCDB131 medium containing 0.2% FBS at 4 × 10^5/mL cell density. One mL of the cell suspension was then transferred to microfuge tubes and incubated with 30 μM PD98059 for 0.5 h at room temperature prior to the addition of 12.5 ng/mL FGF-2 or 0.1 μM of each of the compounds **1**, *ent*-**1**, **2**, and *ent*-**2** (final concentrations). Alternately, 1 mL of cell suspension was incubated with FGF-2 alone (12.5 ng/mL) or each neolignan (0.1 μM). The suspensions were gently mixed (pipetting up and down three times), and 100 μL (4 × 10^4 cells) was aliquoted into a 96 well plate that had been pre-coated overnight at 4 °C with Matrigel basement membrane matrix. The plates were incubated at 37 °C, and the cells in each well were photographed (under 40× magnification) 4 h after seeding. Microtubules were counted using Image J software. Each treatment was performed in triplicate, and four independent experiments were performed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01459.

^{1}H and ^{13}C NMR spectra of compounds (±)-**1**, **1**, *ent*-**1**, (±)-**2**, **2**, *ent*-**2**, **4**−**7** (and precursors), **9**, **10**, **14**, **15**, **17** (and precursor), **18**−**23** and ^{1}H NMR spectra of compounds *ent*-**15**, *ent*-**17** (and precursor), and *ent*-**18**−*ent*-**23** (PDF)

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Notes

The authors declare no competing financial interest.

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■ ADDITIONAL NOTE

[1] It is also possible that the conversion **7** + **8** → **9** proceeds via an S_N1 pathway.

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SUPPORTING INFORMATION FOR:

Developing Neolignans as Pro-Angiogenic Agents:
Stereoselective Total Syntheses and Preliminary Biological Evaluations of the Four Guaiacylglycerol 8-*O*-4′-Coniferyl Ethers

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Figure S1. 300 MHz ^{1}H NMR Spectrum of Compound (±)-**1** [recorded in $(CD_3)_2CO$]

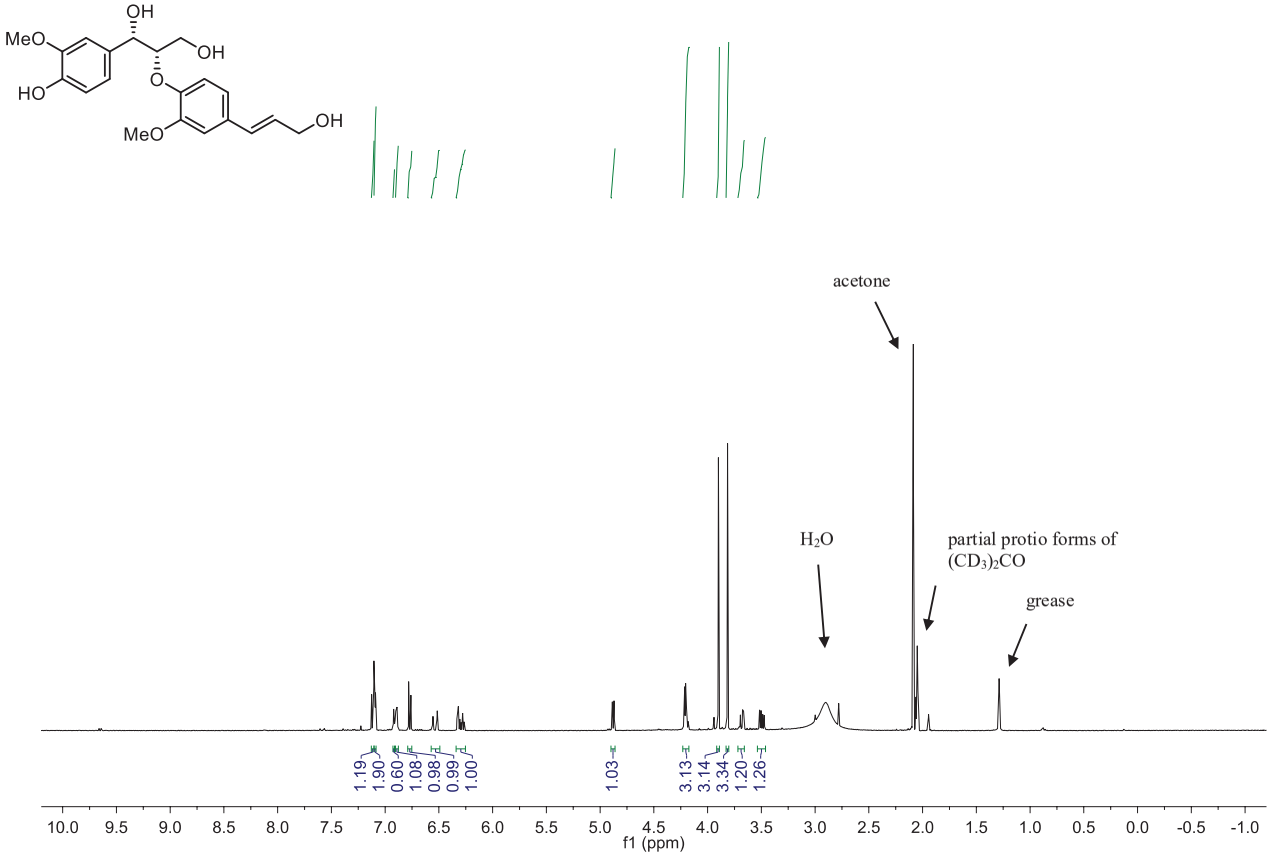


Figure S2. 400 MHz ^{1}H NMR Spectrum of Compound (±)-**1** (recorded in CD_3OD)

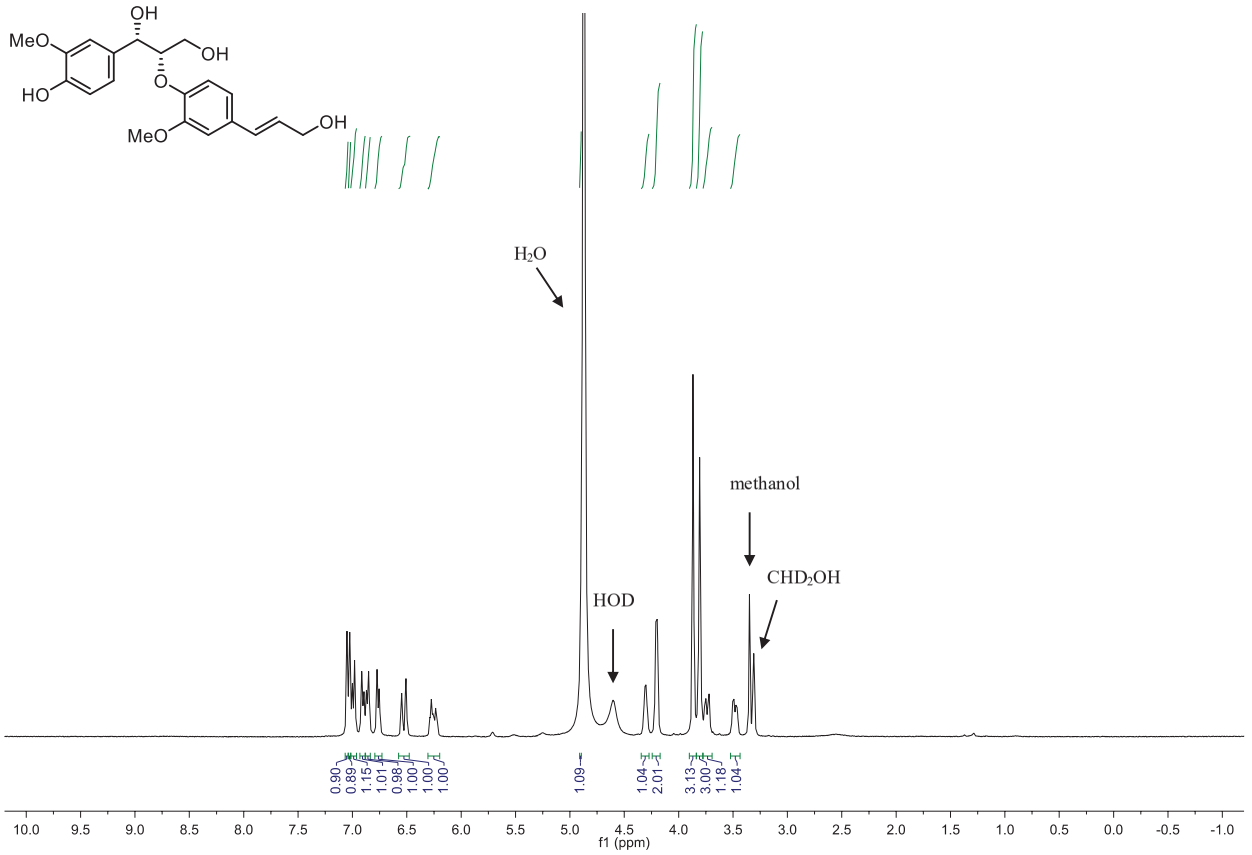


Figure S3. 100 MHz ^{13}C NMR Spectrum of Compound (±)-**1** (recorded in CD_3OD)

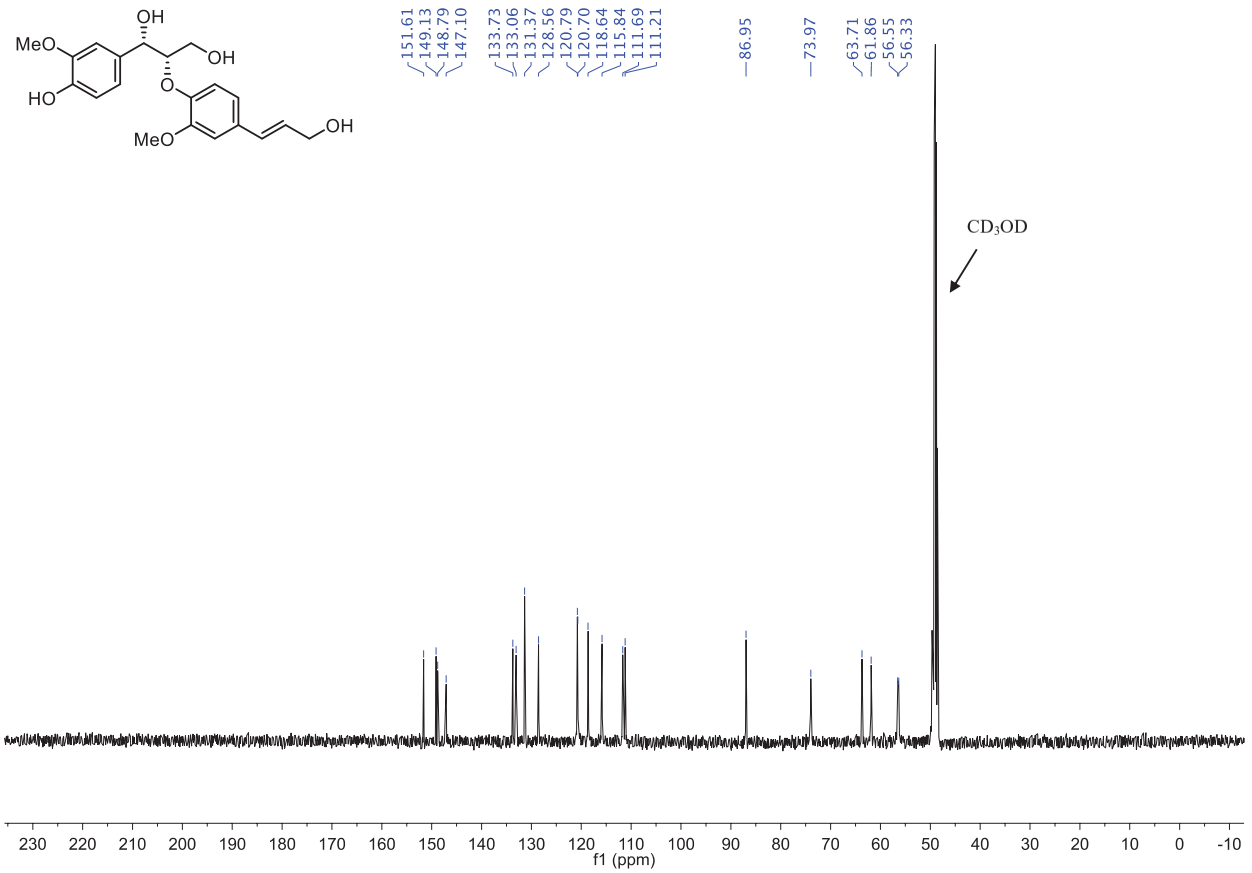


Figure S4. 400 MHz ^{1}H NMR Spectrum of Compound **1** (recorded in CD_3OD)

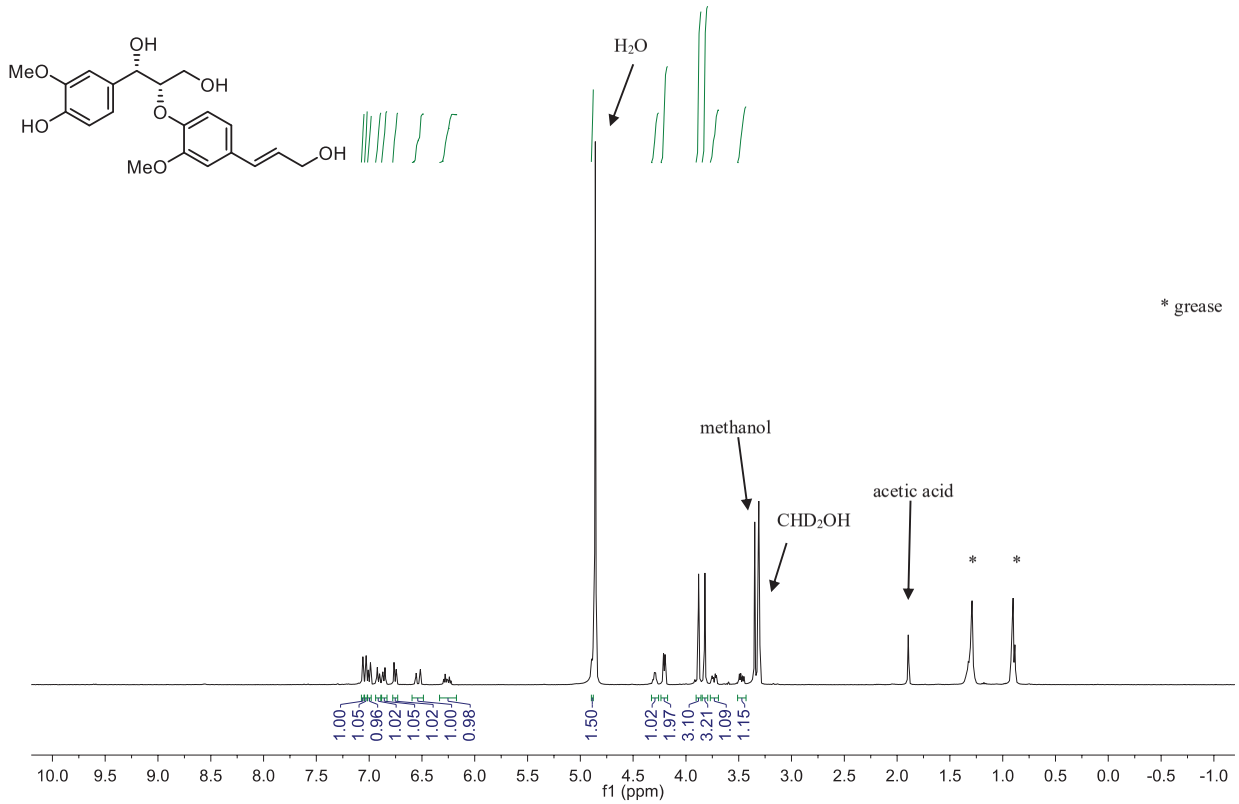


Figure S5. 100 MHz ^{13}C NMR Spectrum of Compound **1** (recorded in CD_3OD)

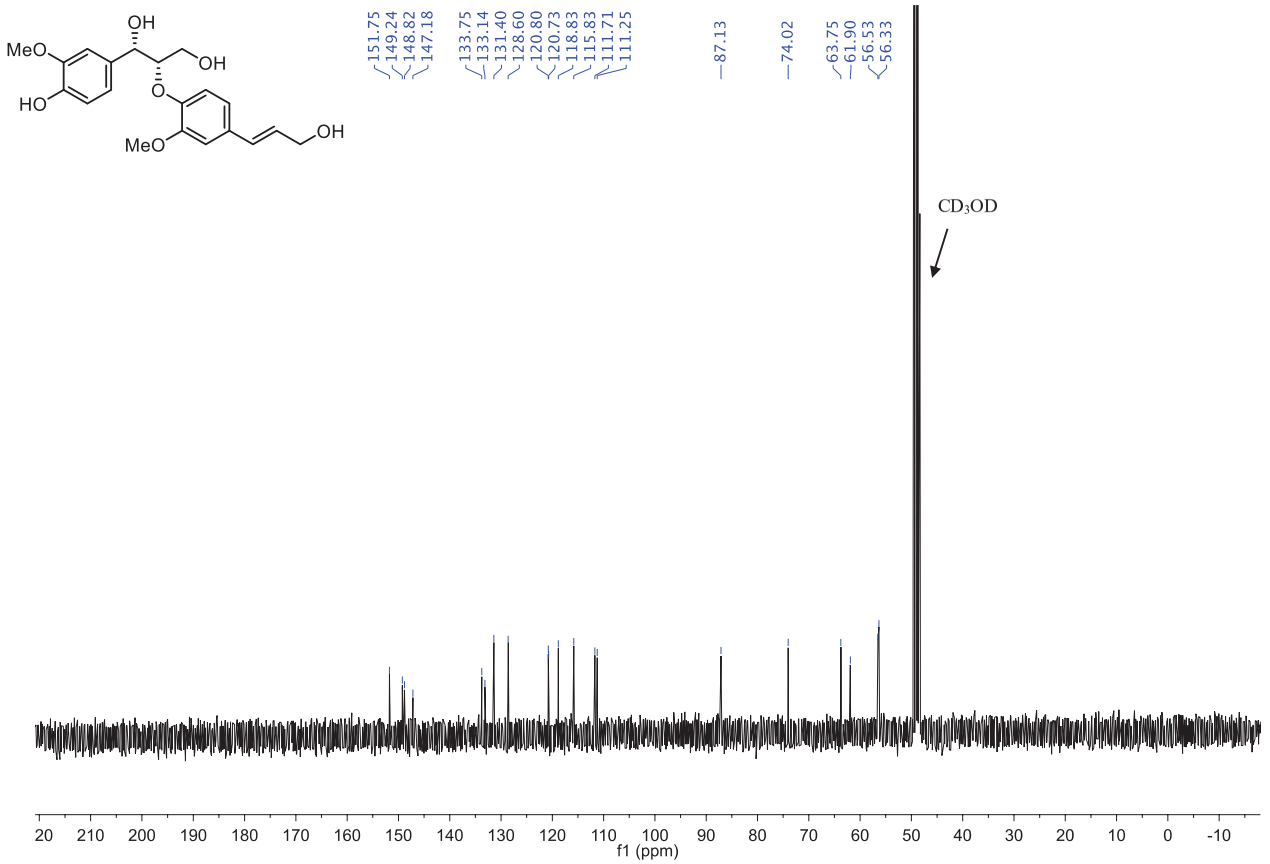


Figure S6. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**1** (recorded in CD_3OD)

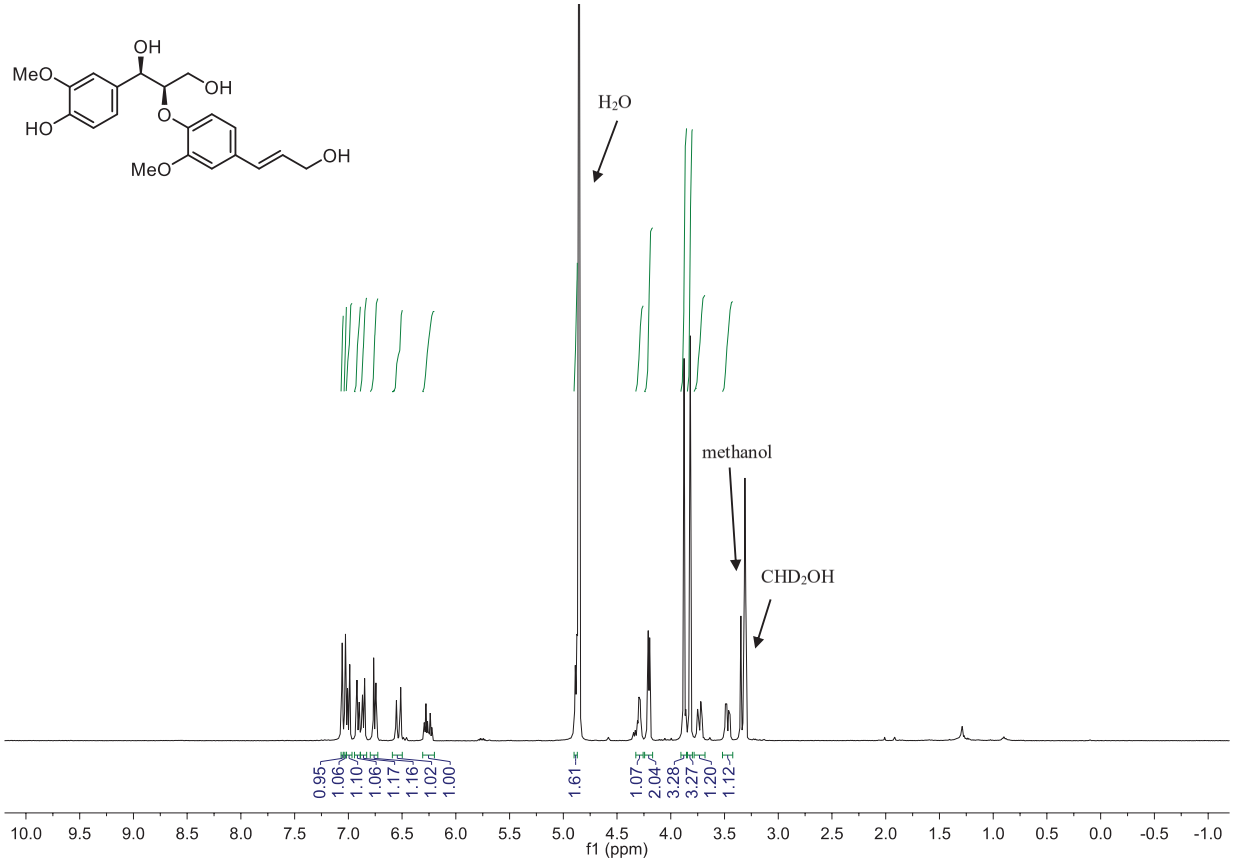


Figure S7. 100 MHz ^{13}C NMR Spectrum of Compound *ent*-**1** (recorded in CD_3OD)

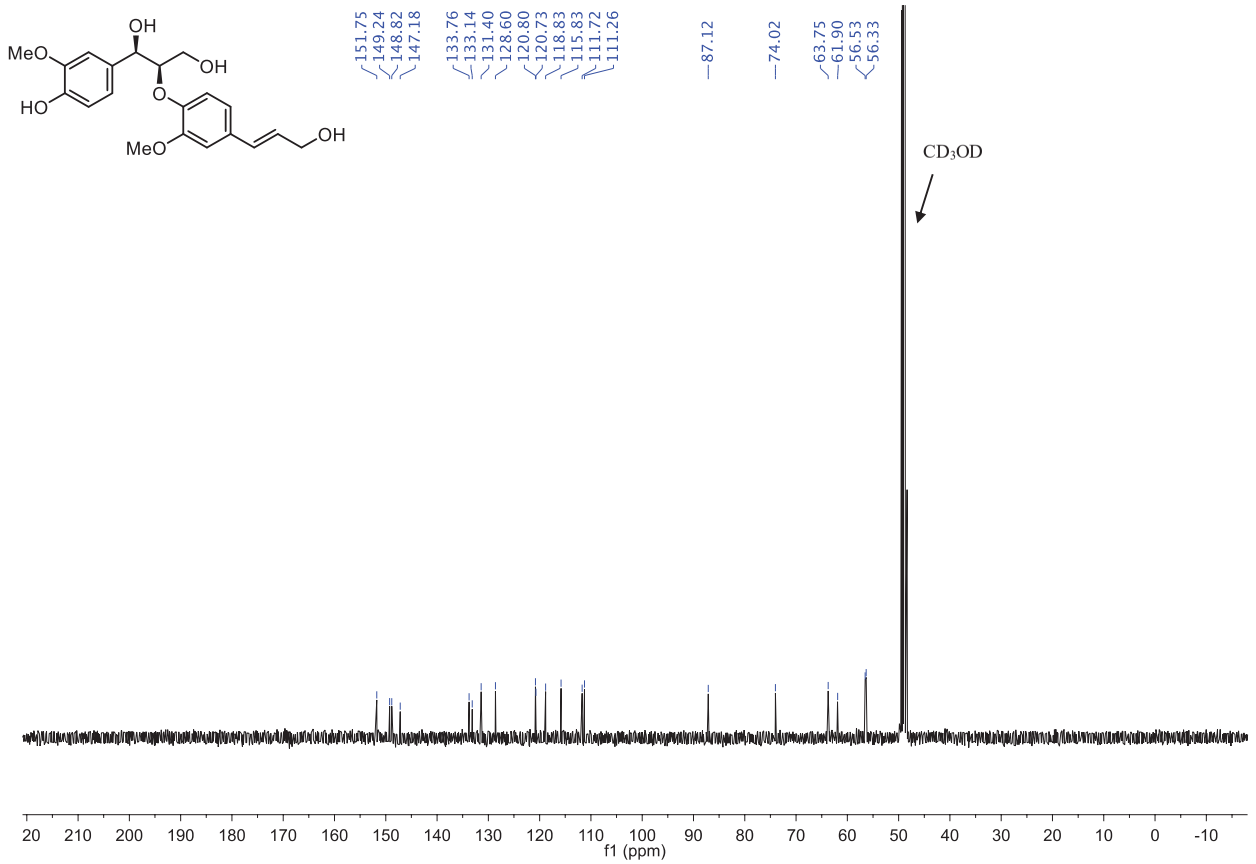


Figure S8. 300 MHz ^{1}H NMR Spectrum of Compound (±)-**2** [recorded in $(CD_3)_2CO$]

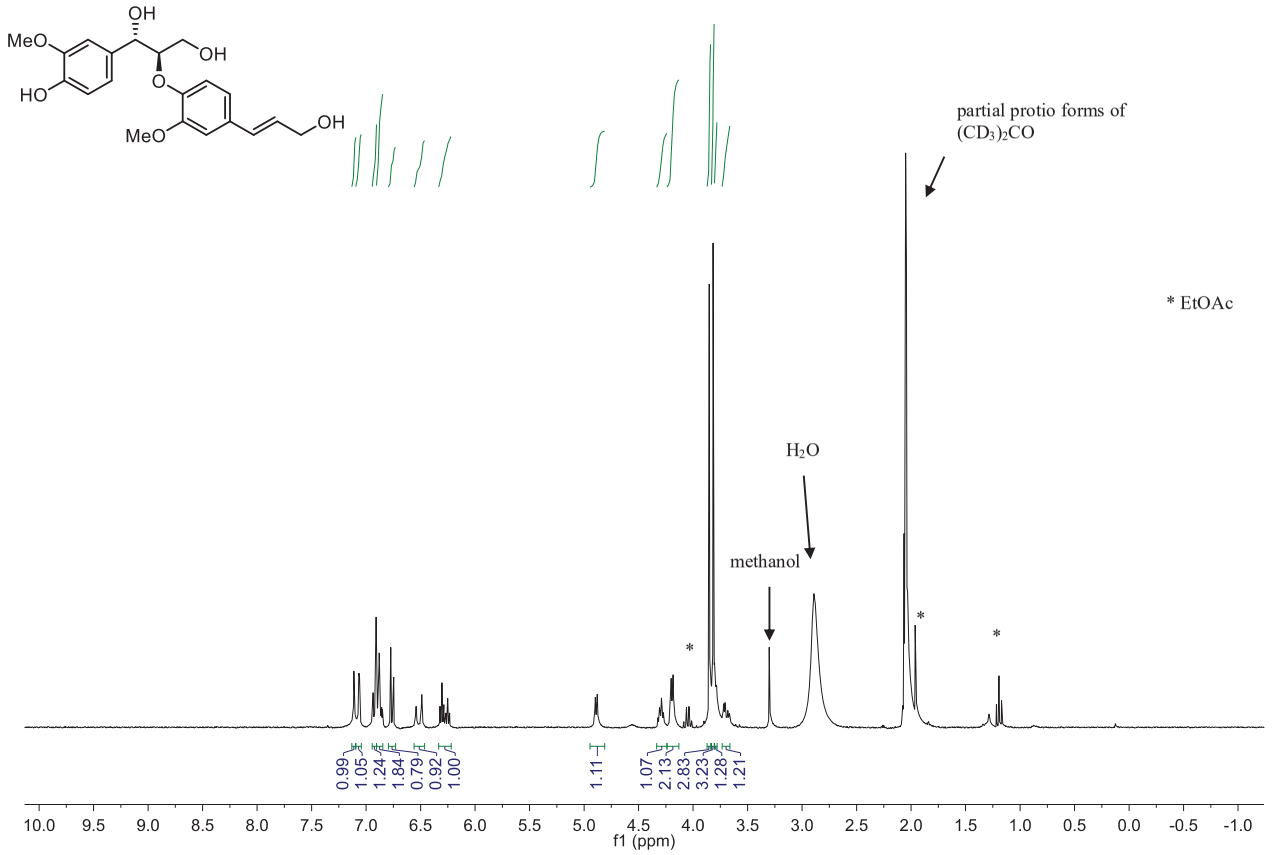


Figure S9. 400 MHz ^{1}H NMR Spectrum of Compound (±)-**2** (recorded in CD_3OD)

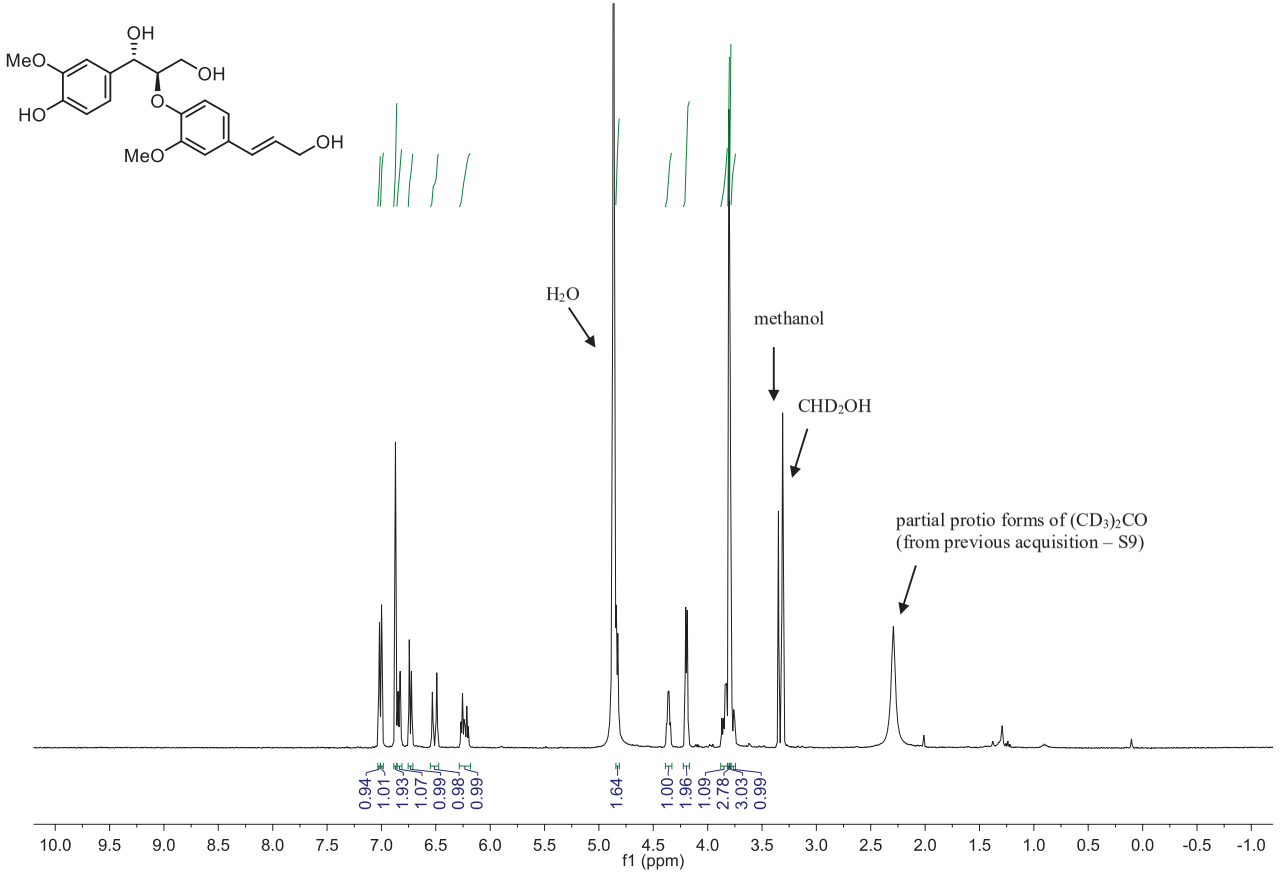


Figure S10. 100 MHz ^{13}C NMR Spectrum of Compound (±)-**2** (recorded in CD_3OD)

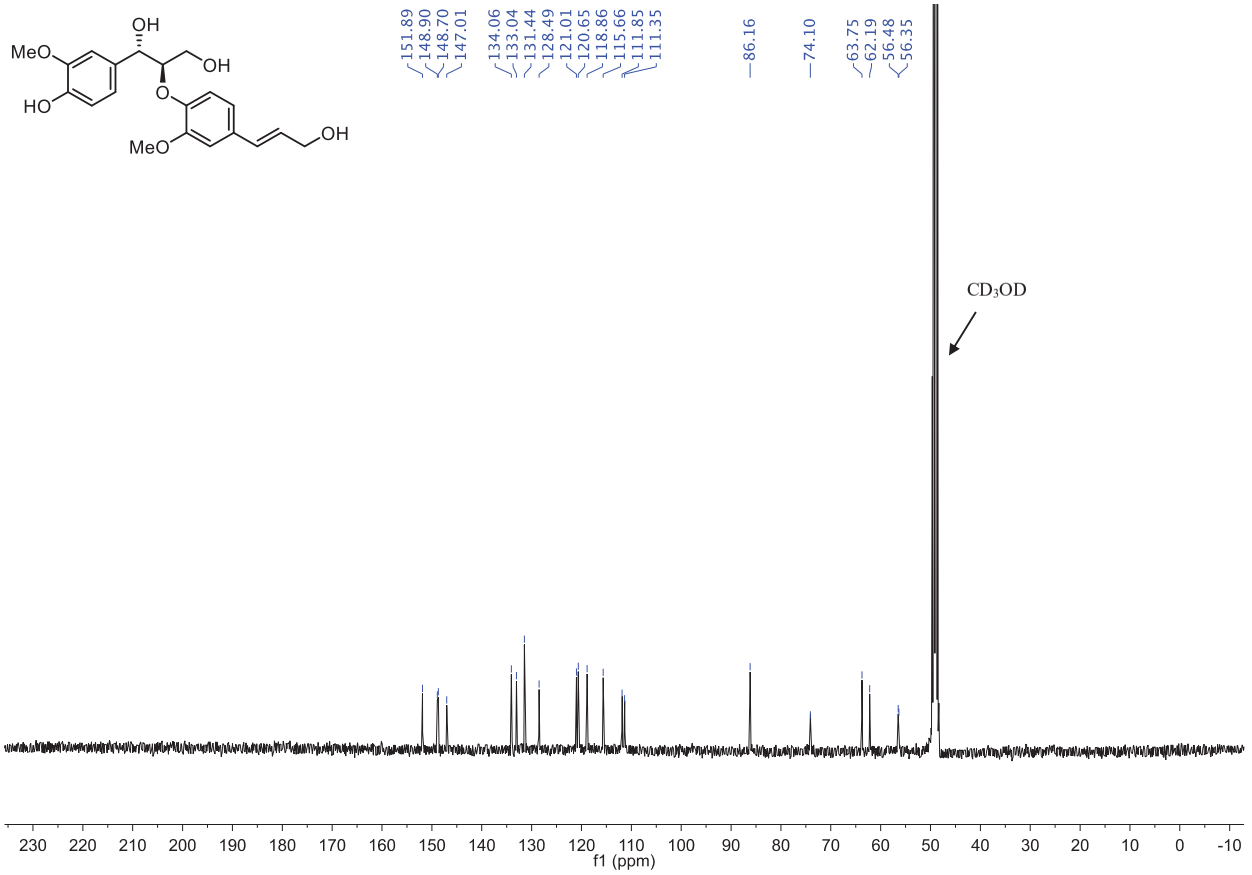


Figure S11. 400 MHz ^{1}H NMR Spectrum of Compound **2** (recorded in CD_3OD)

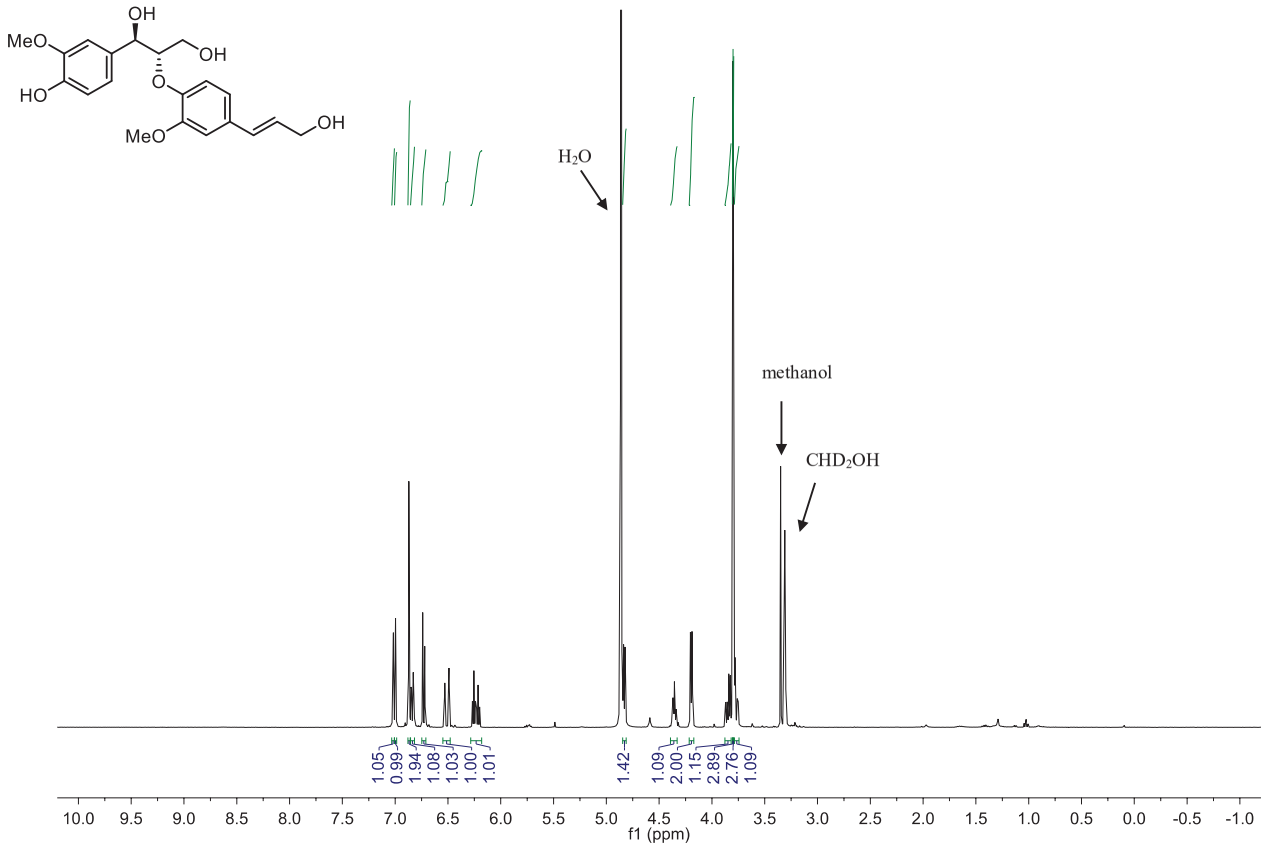


Figure S12. 600 MHz ^{1}H NMR Spectrum of Compound **2** [recorded in $(CD_3)_2SO$]

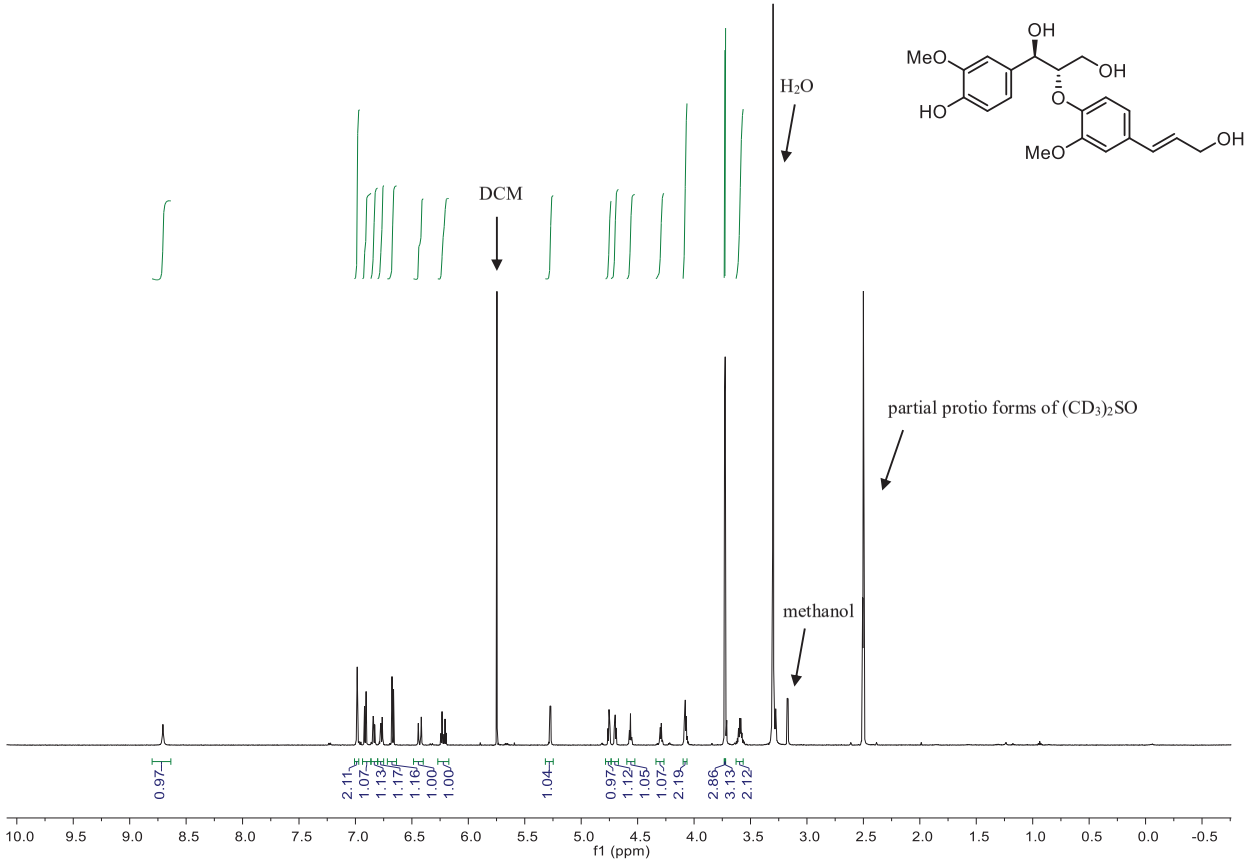


Figure S13. 100 MHz ^{13}C NMR Spectrum of Compound **2** (recorded in CD_3OD)

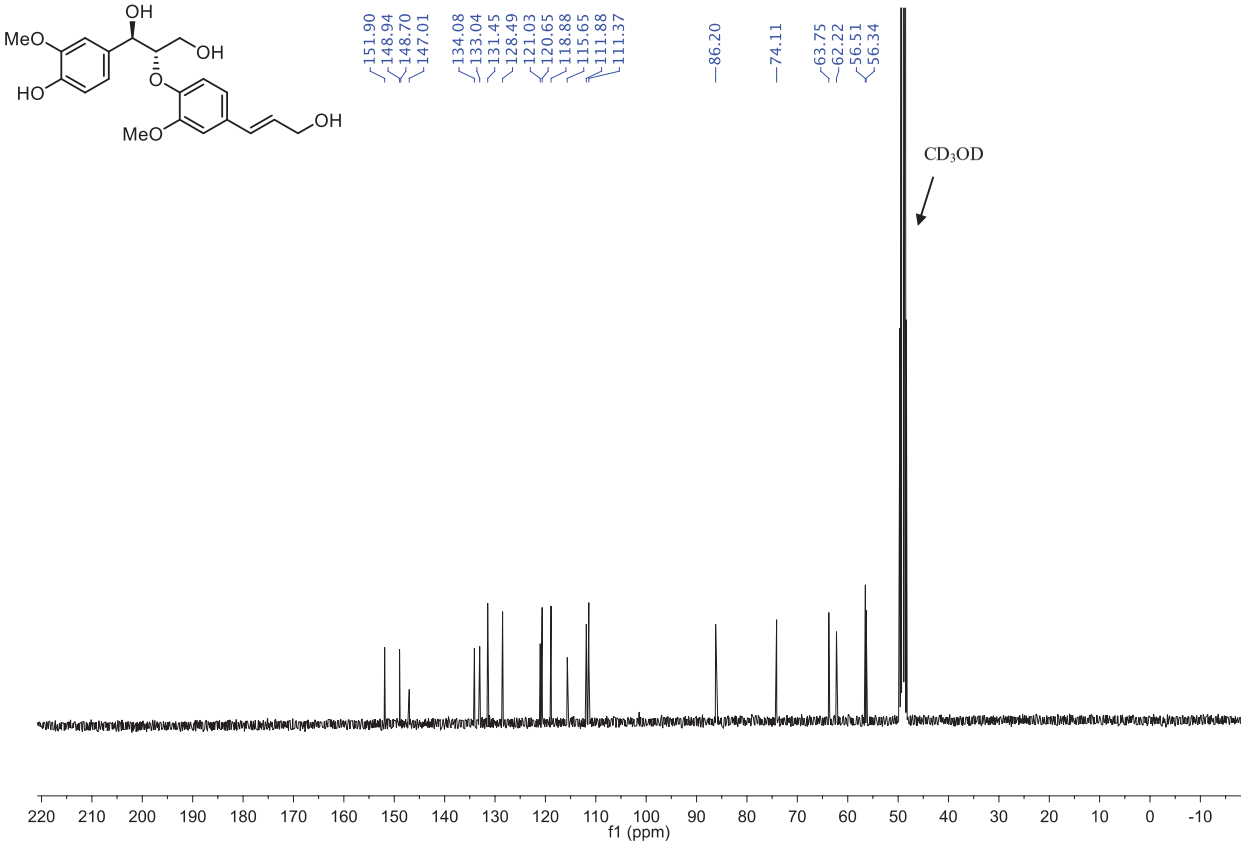


Figure S14. 150 MHz ^{13}C NMR Spectrum of Compound **2** [recorded in $(CD_3)_2SO$]

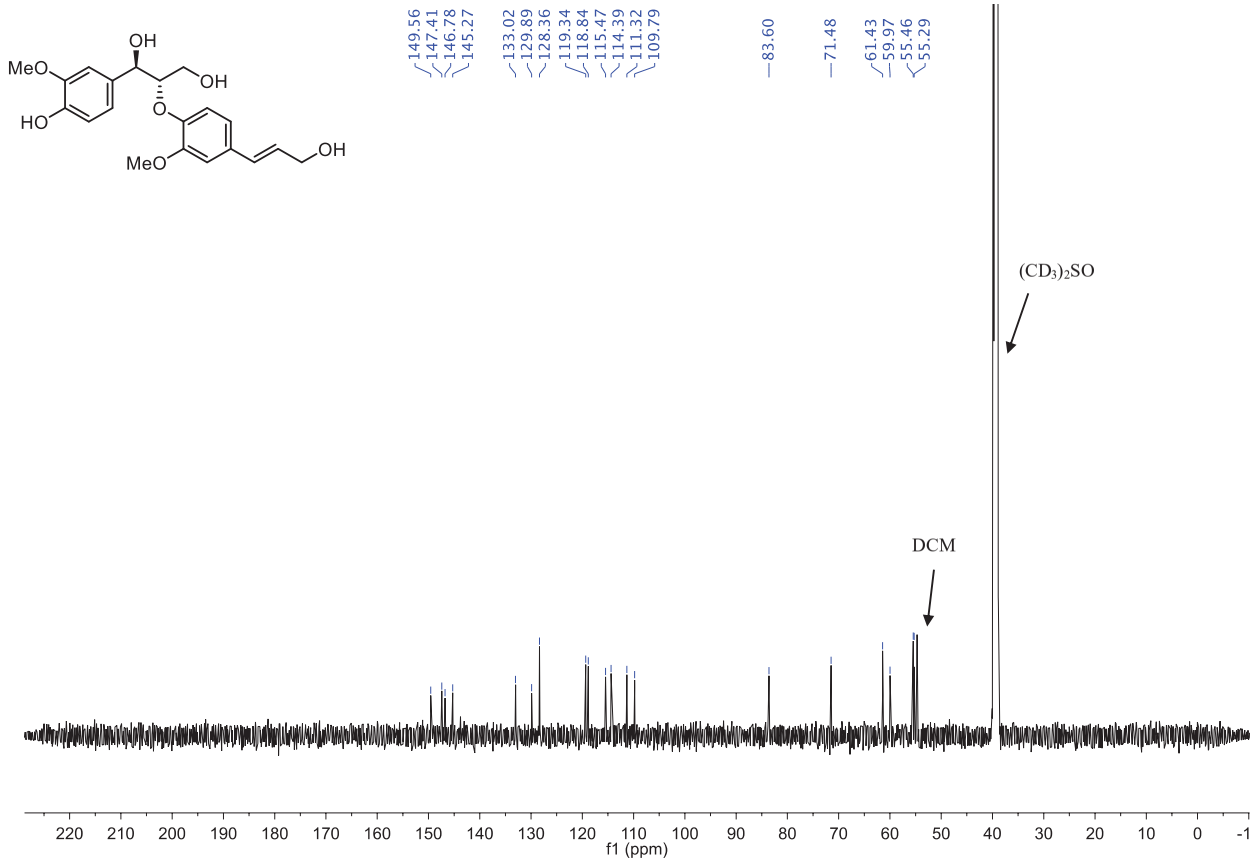


Figure S15. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**2** (recorded in CD_3OD)

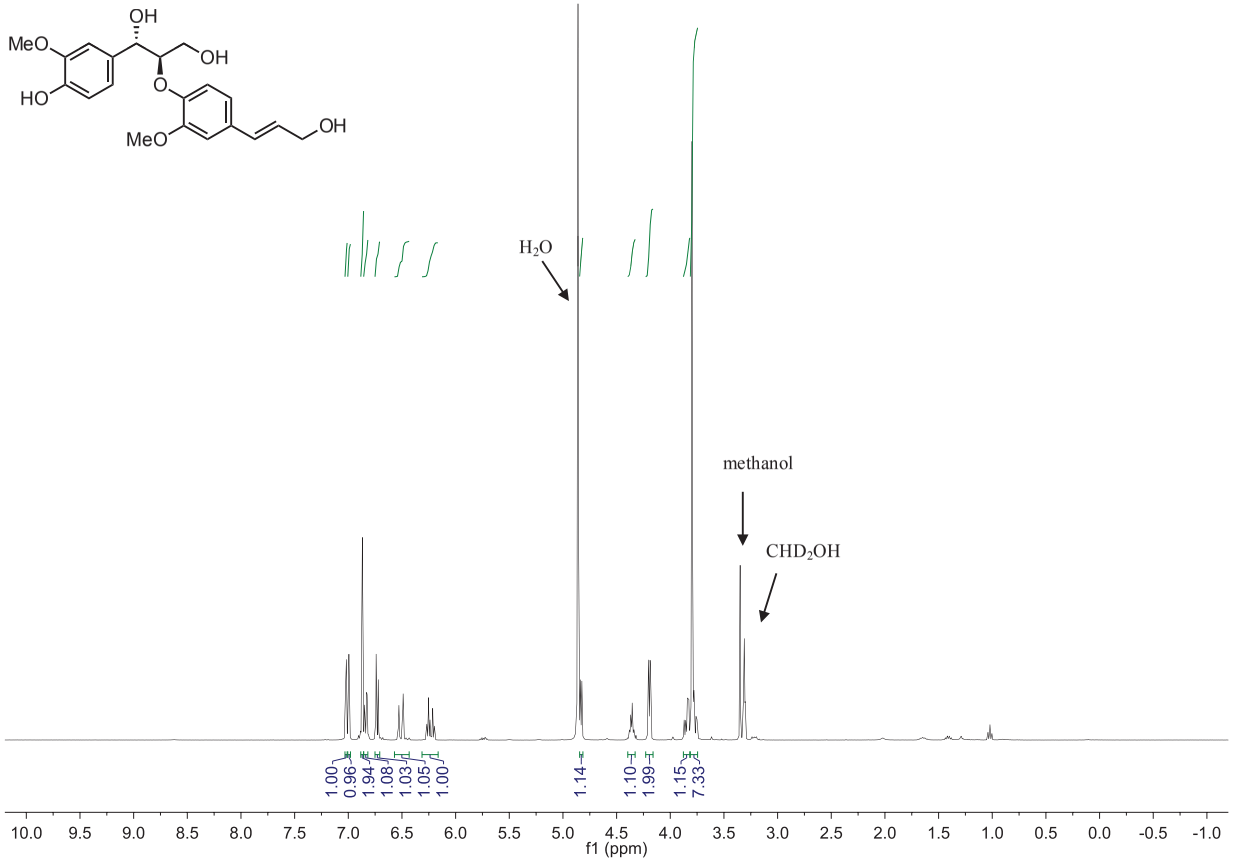


Figure S16. 100 MHz ^{13}C NMR Spectrum of Compound *ent*-**2** (recorded in CD_3OD)

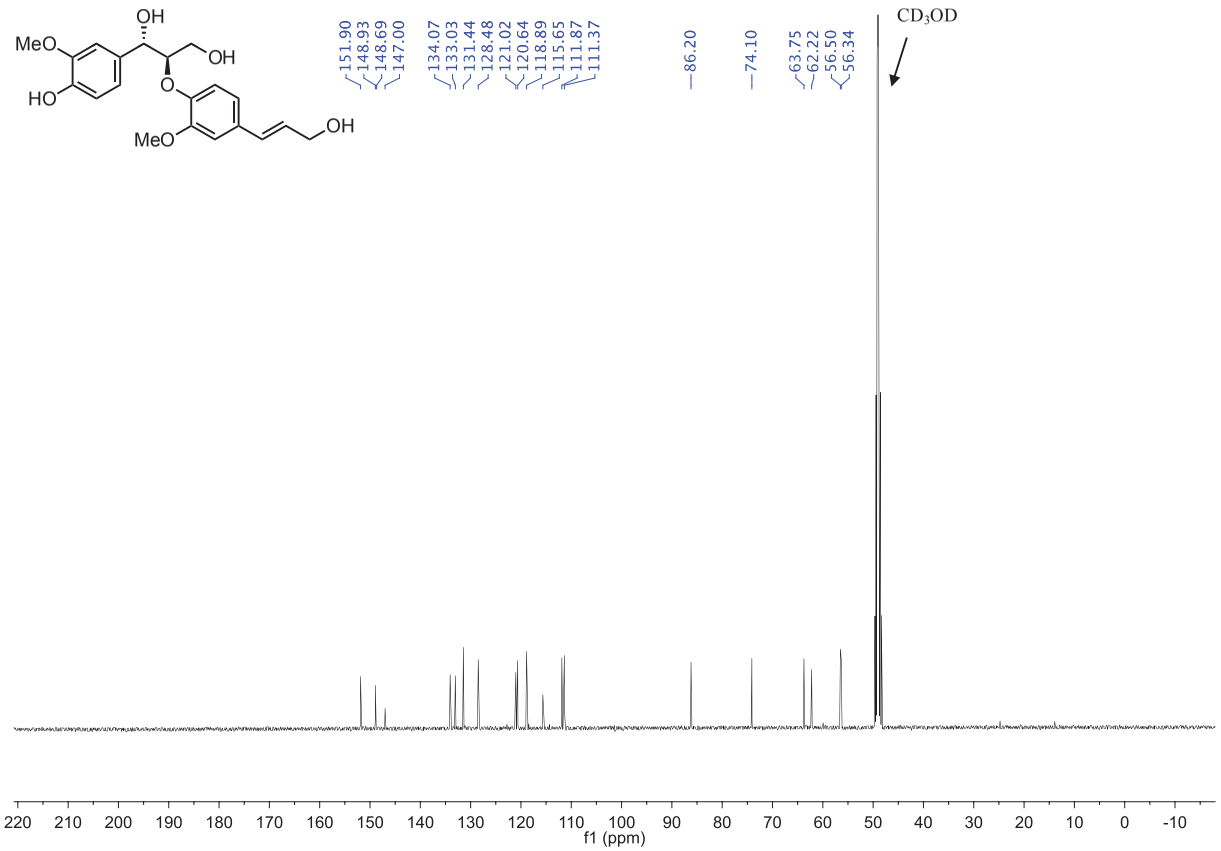


Figure S17. 300 MHz ^{1}H NMR Spectrum of Precursor to Compound **4** (Step i) (recorded in $CDCl_3$)

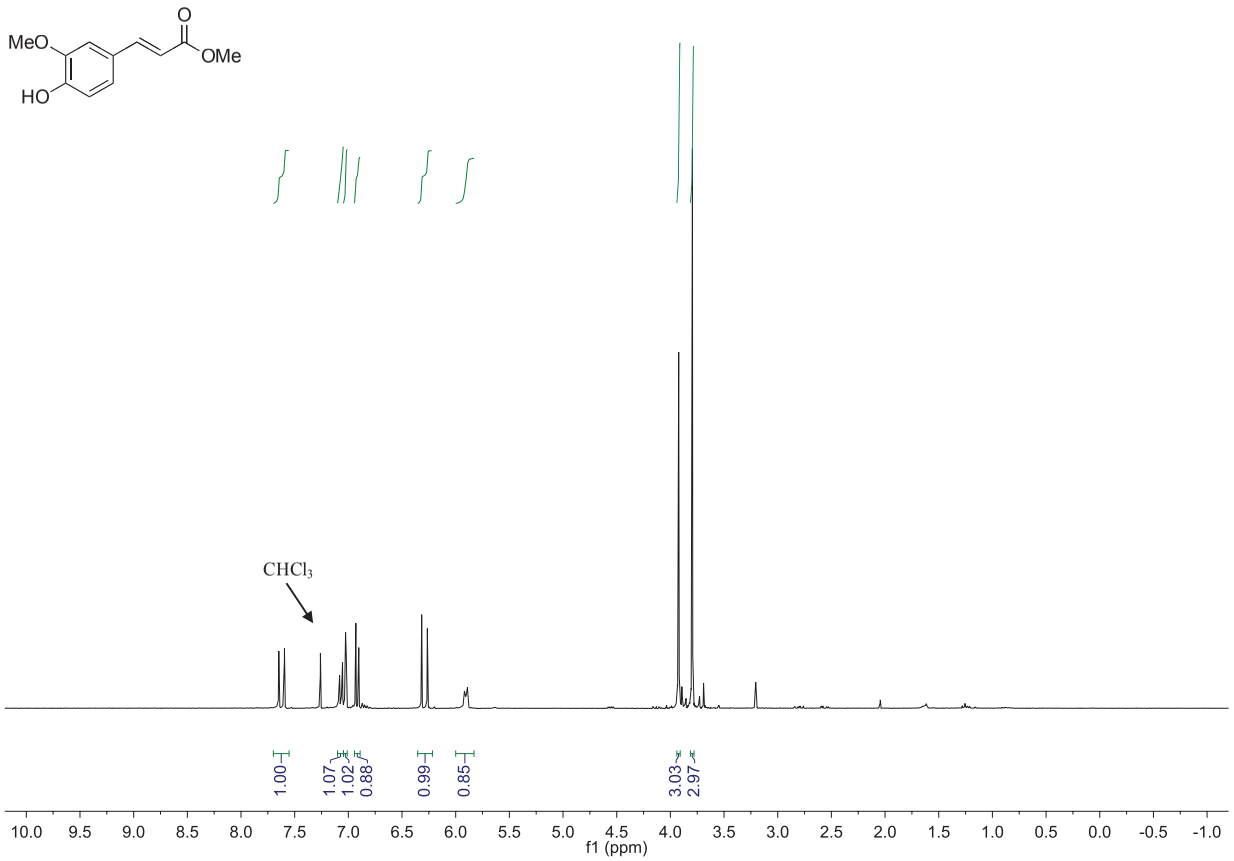


Figure S18. 100 MHz ^{13}C NMR Spectrum of Precursor to Compound **4** (Step i) (recorded in $CDCl_3$)

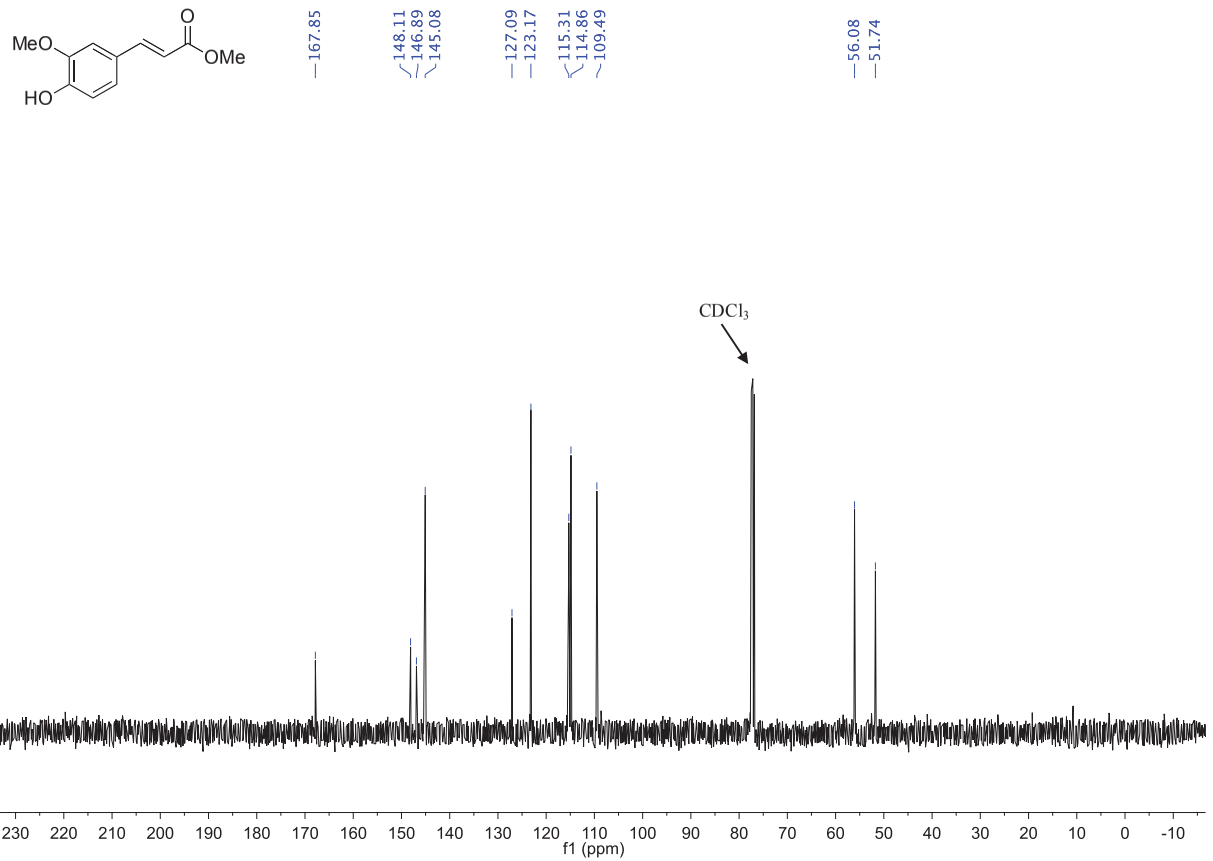


Figure S19. 400 MHz ^{1}H NMR Spectrum of Precursor to Compound **4** (Step ii) (recorded in $CDCl_3$)

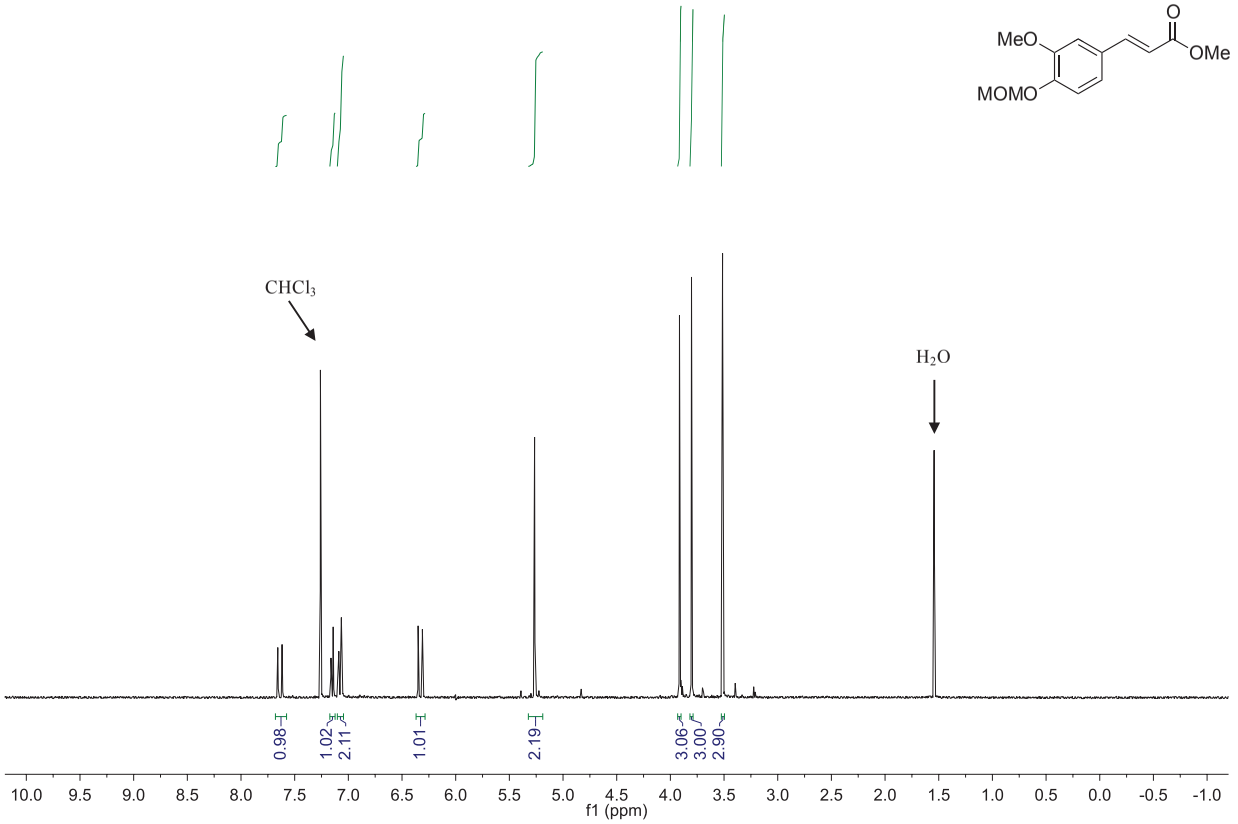


Figure S20. 100 MHz ^{13}C NMR Spectrum of Precursor to Compound **4** (Step ii) (recorded in $CDCl_3$)

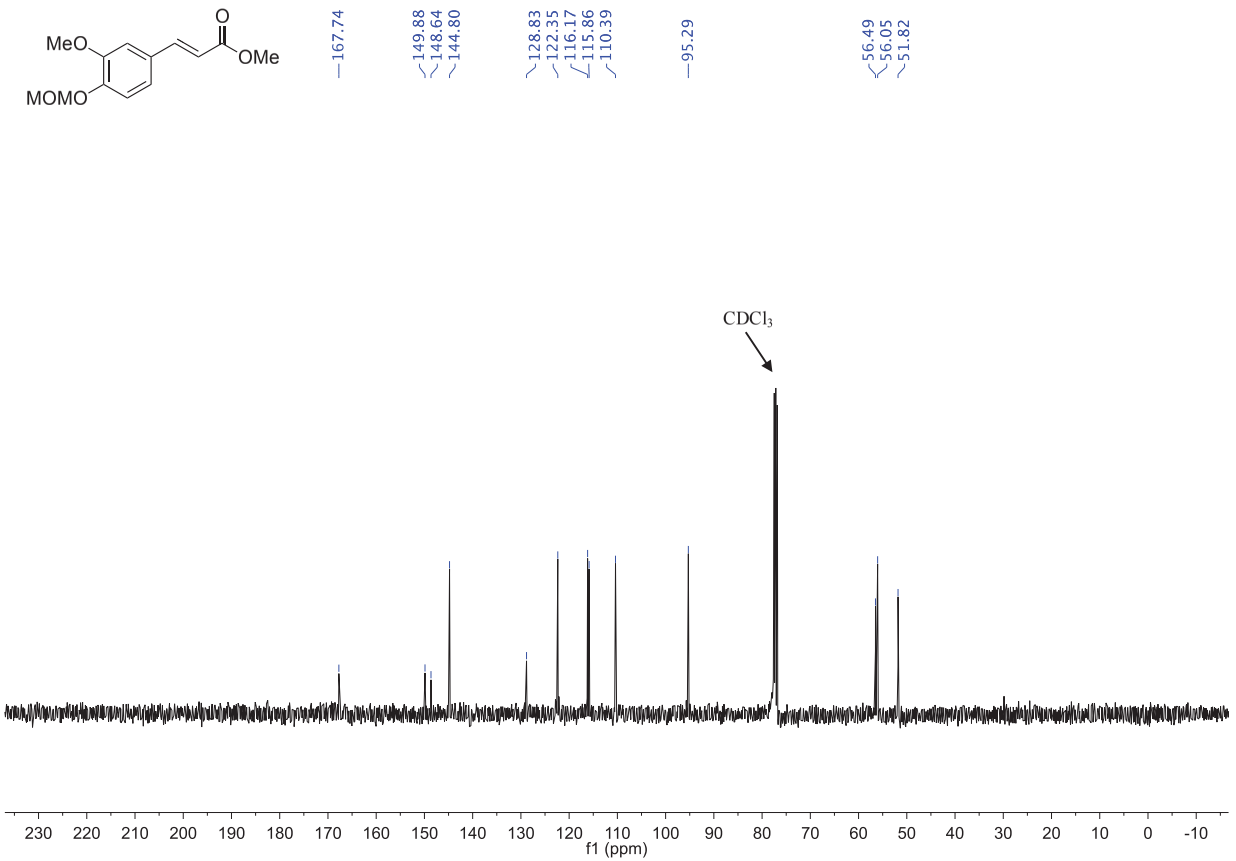


Figure S21. 400 MHz ^{1}H NMR Spectrum of Precursor to Compound **4** (Step iii) (recorded in $CDCl_3$)

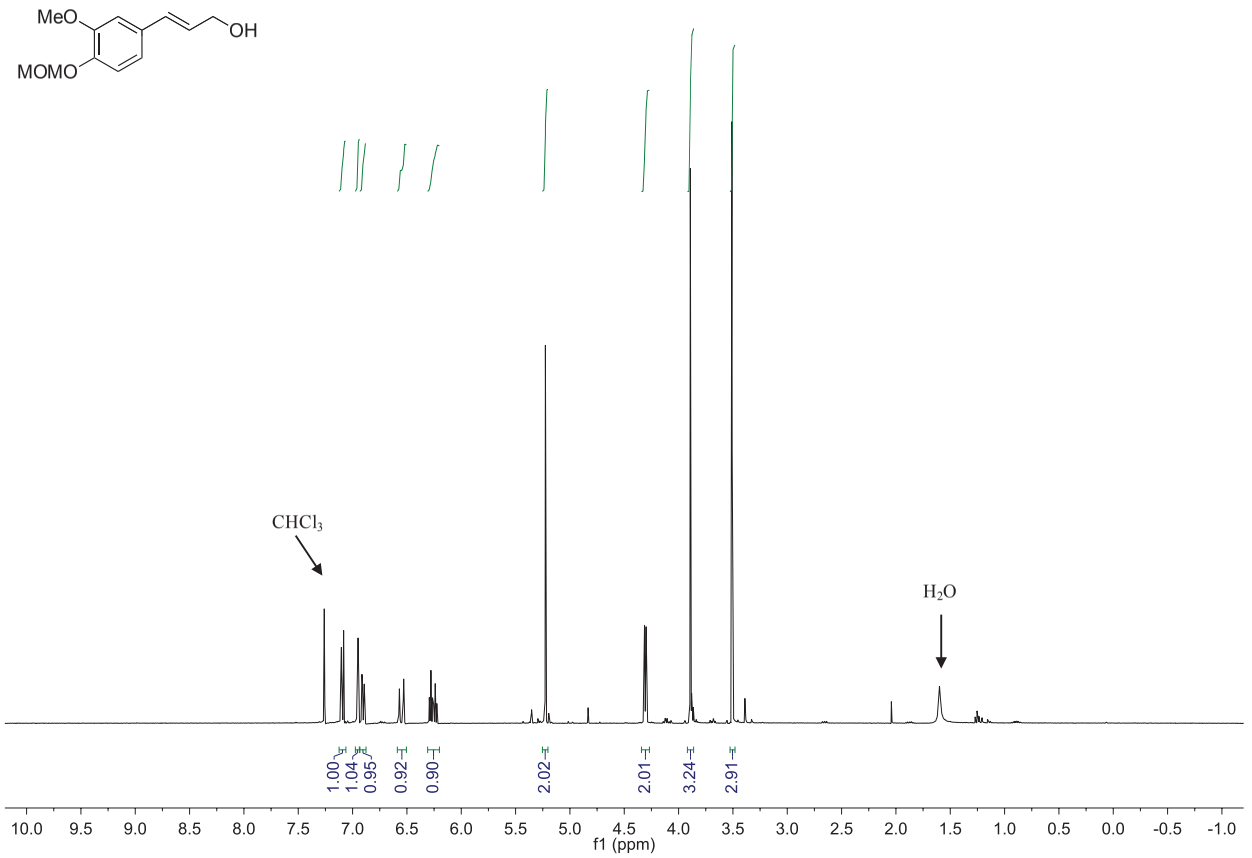


Figure S22. 100 MHz ^{13}C NMR Spectrum of Precursor to Compound **4** (Step iii) (recorded in $CDCl_3$)

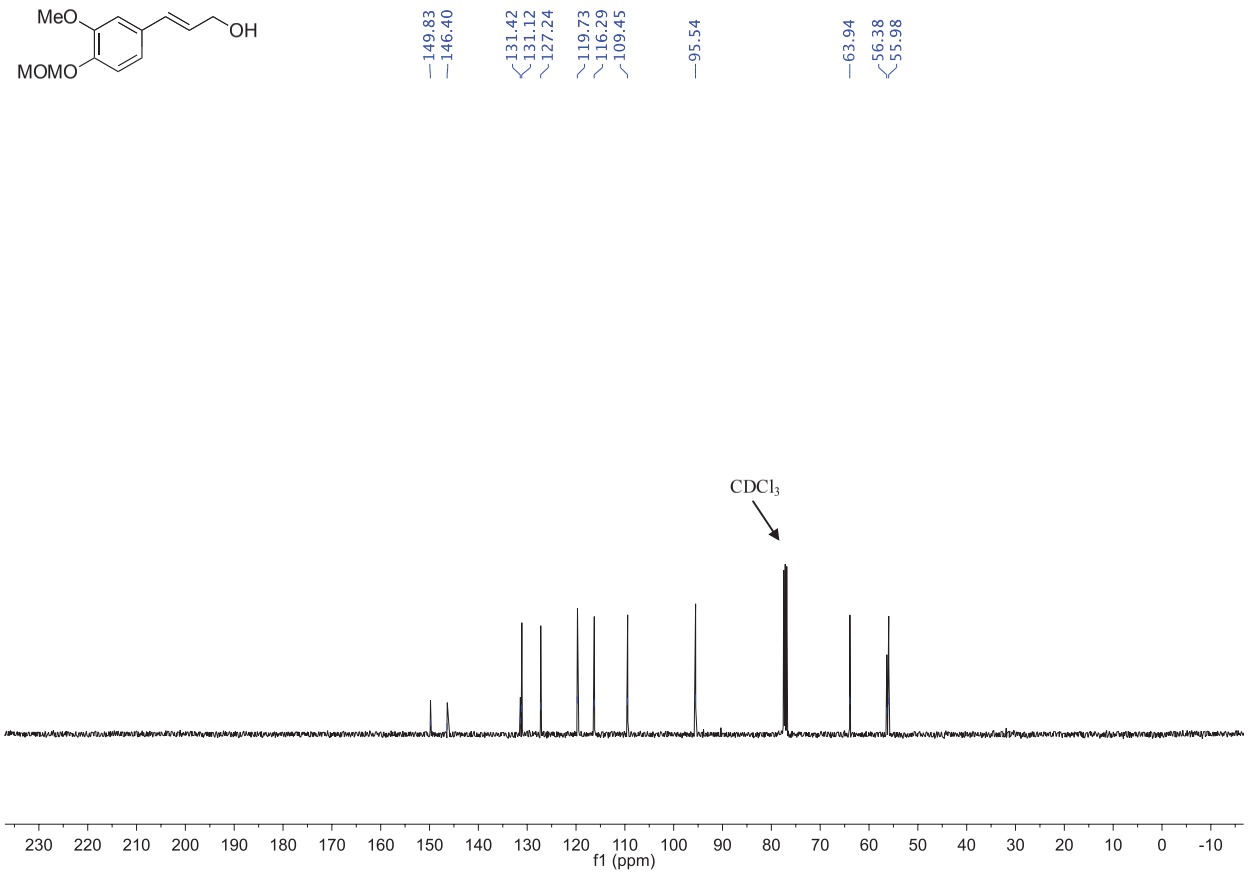


Figure S23. 300 MHz ^{1}H NMR Spectrum of Compound **4** (recorded in $CDCl_3$)

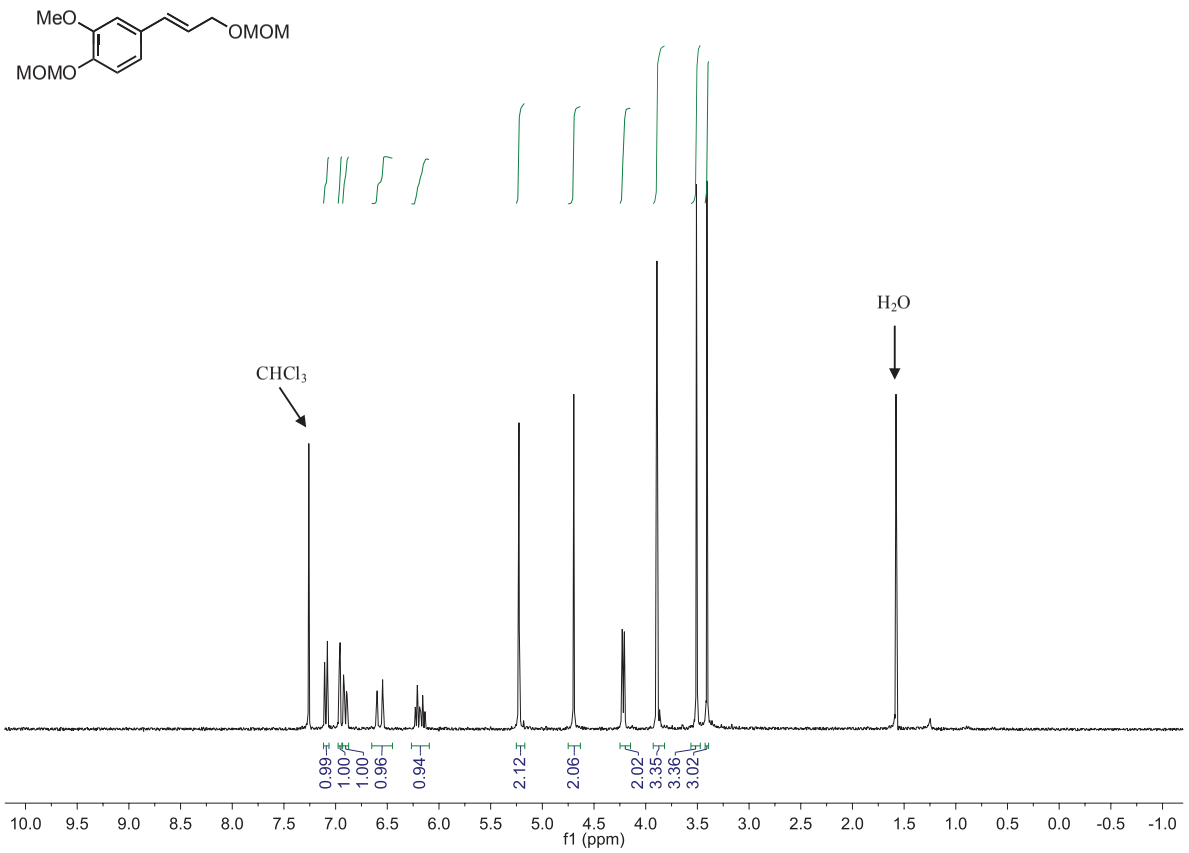


Figure S24. 100 MHz ^{13}C NMR Spectrum of Compound **4** (recorded in $CDCl_3$)

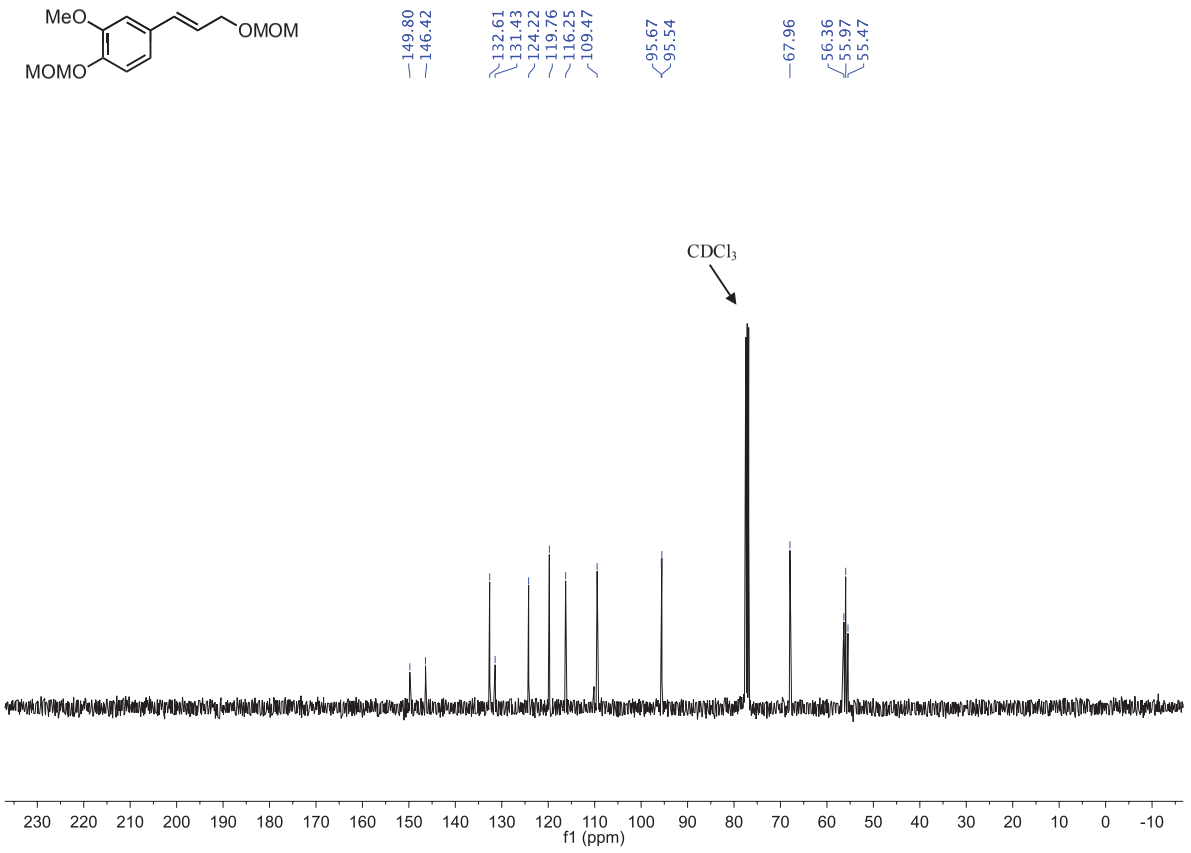


Figure S25. 400 MHz ^{1}H NMR Spectrum of Compound **5** (recorded in $CDCl_3$)

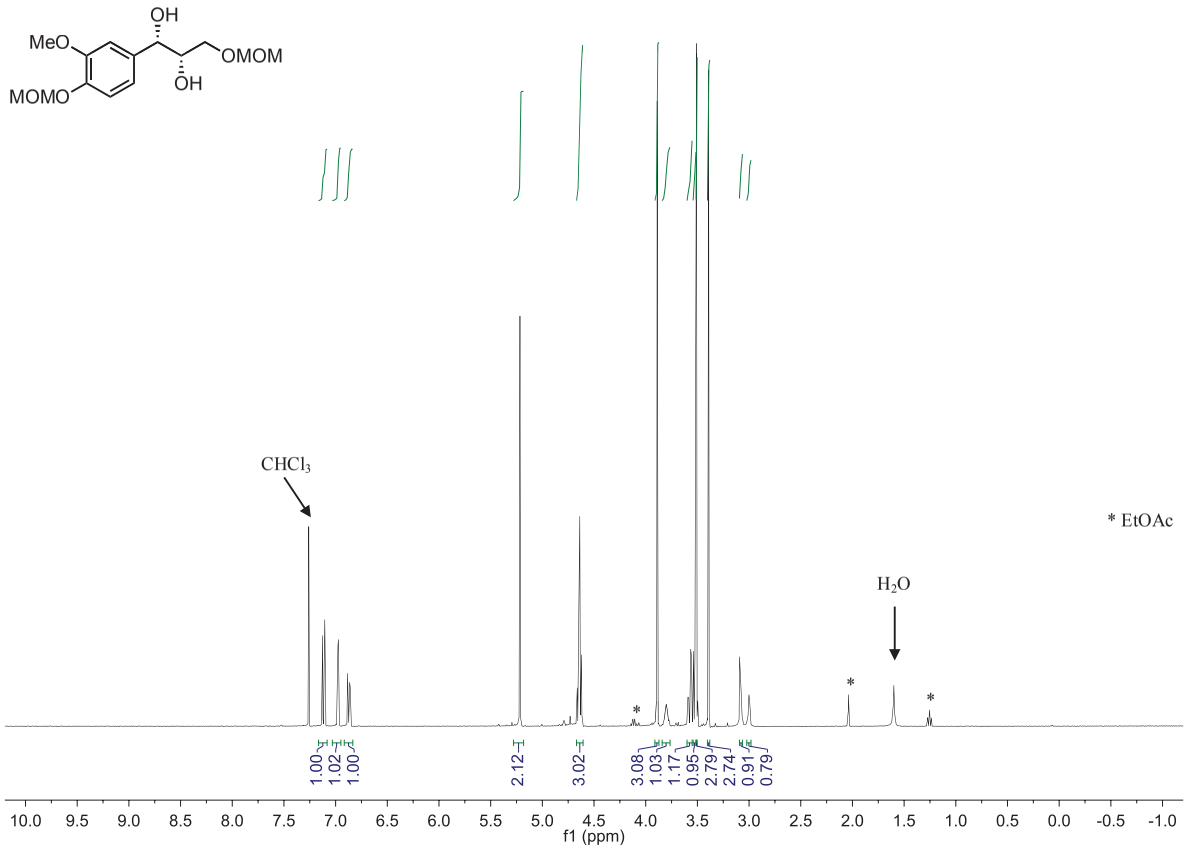


Figure S26. 100 MHz ^{13}C NMR Spectrum of Compound **5** (recorded in $CDCl_3$)

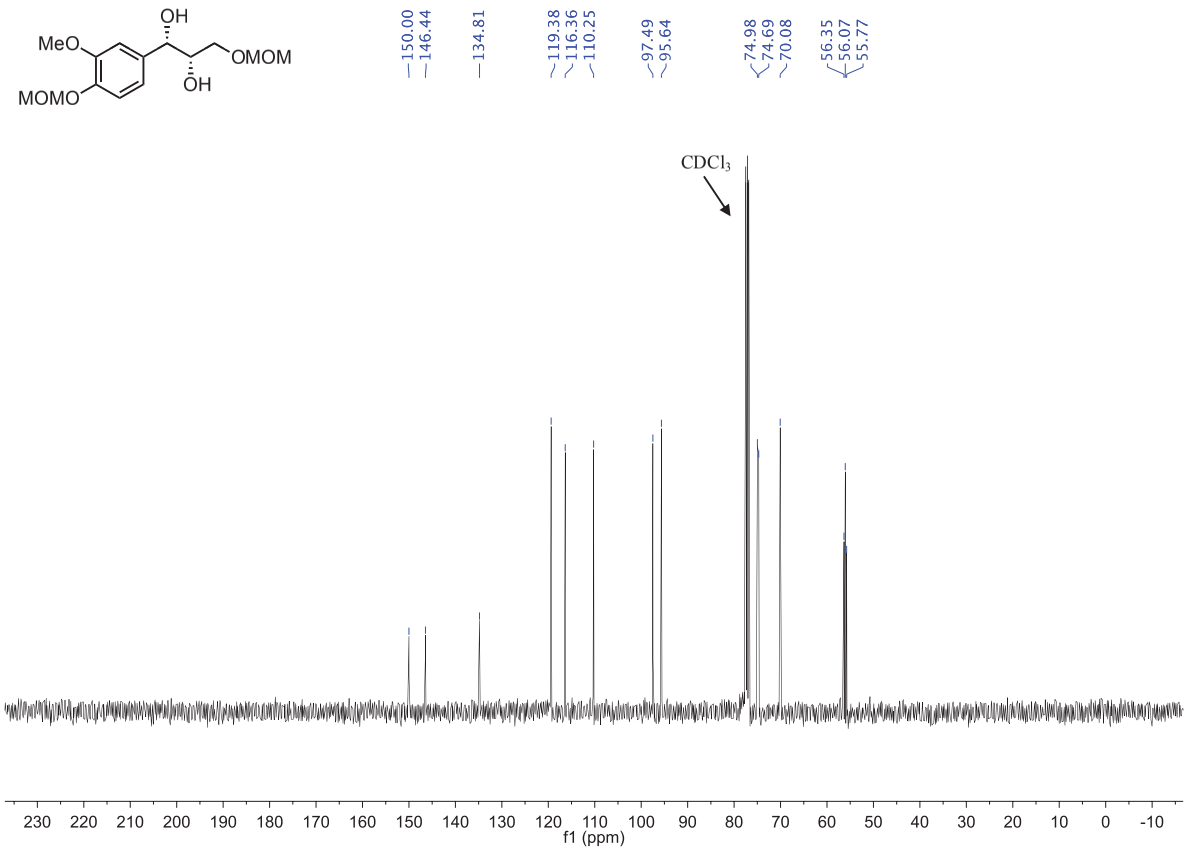


Figure S27. 400 MHz ^{1}H NMR Spectrum of Compound **6** (recorded in $CDCl_3$)

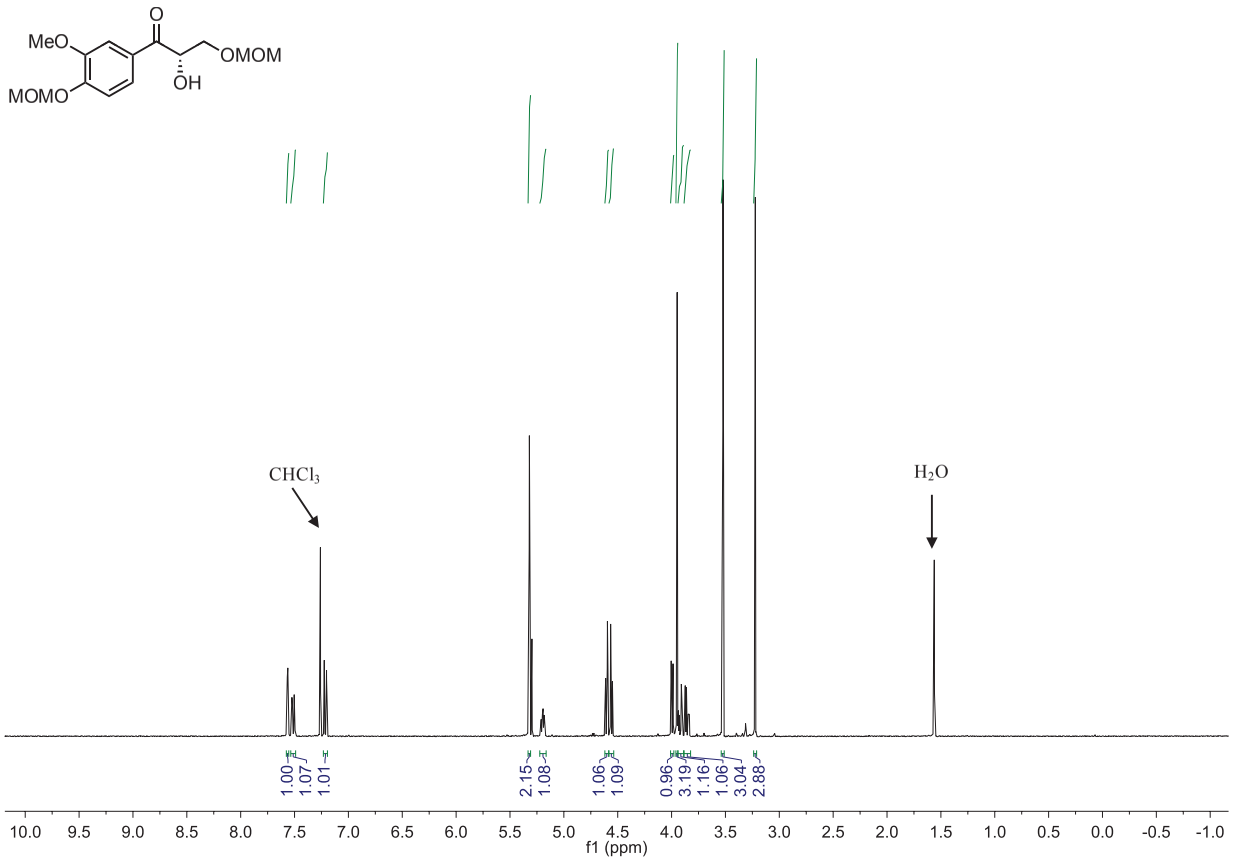


Figure S28. 100 MHz ^{13}C NMR Spectrum of Compound **6** (recorded in $CDCl_3$)

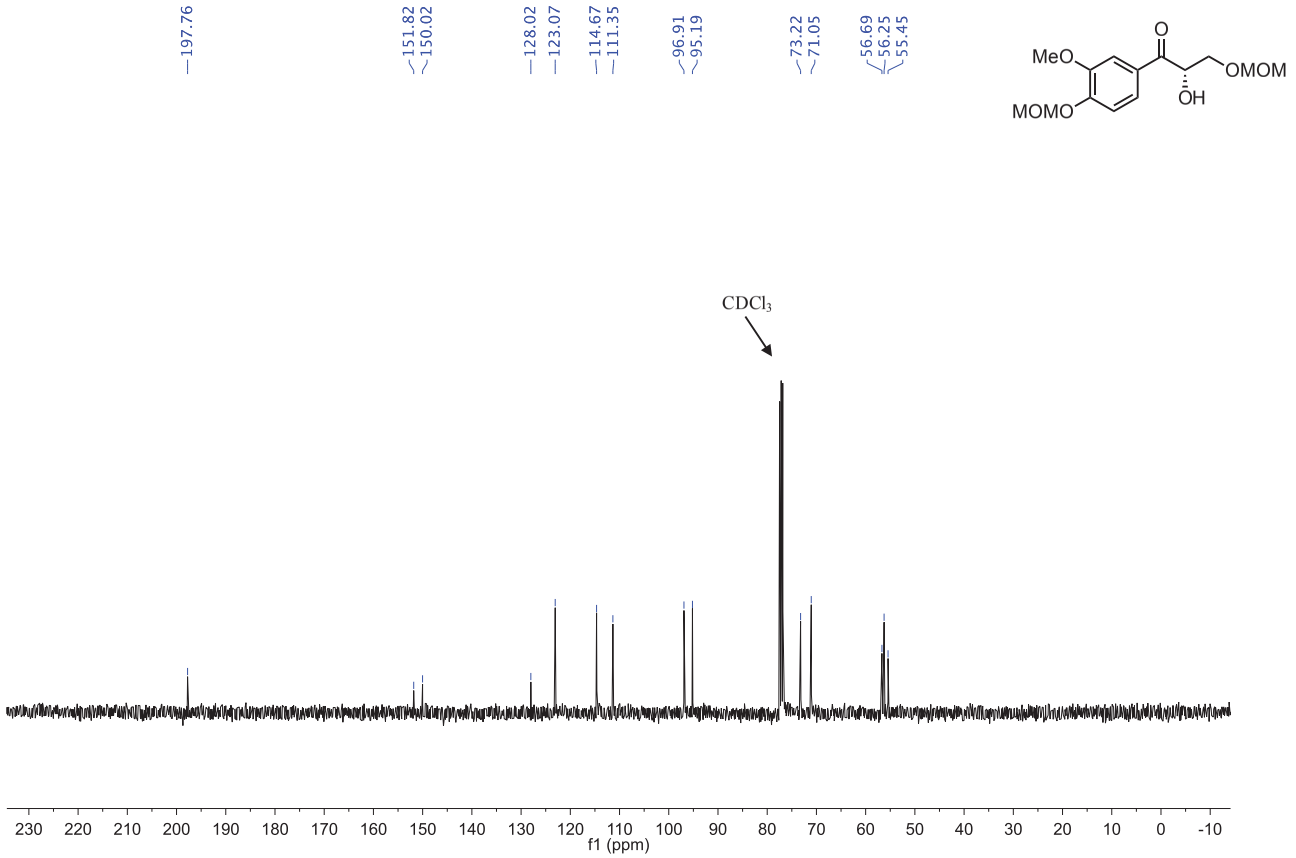


Figure S29. 400 MHz ^{1}H NMR Spectrum of Compound **7** (recorded in $CDCl_3$)

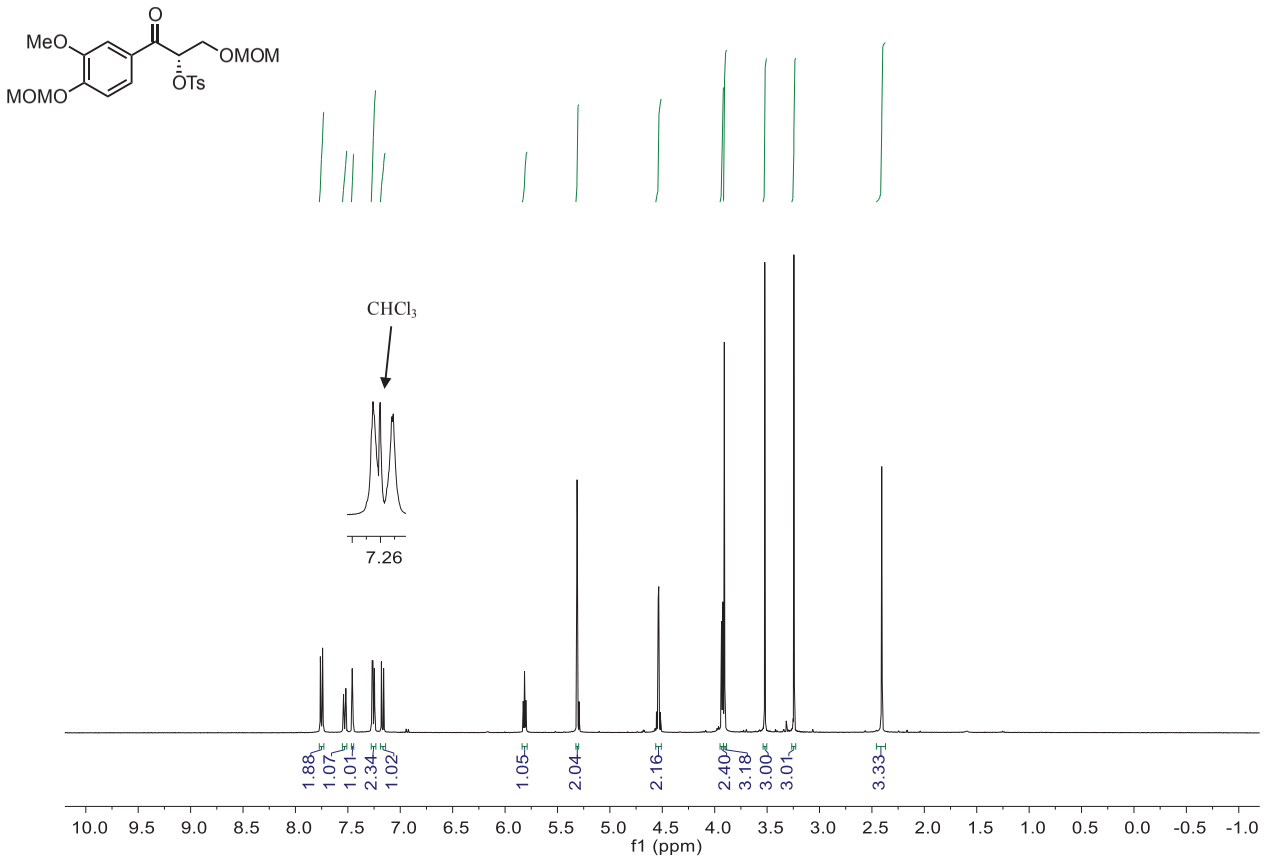


Figure S30. 100 MHz ^{13}C NMR Spectrum of Compound **7** (recorded in $CDCl_3$)

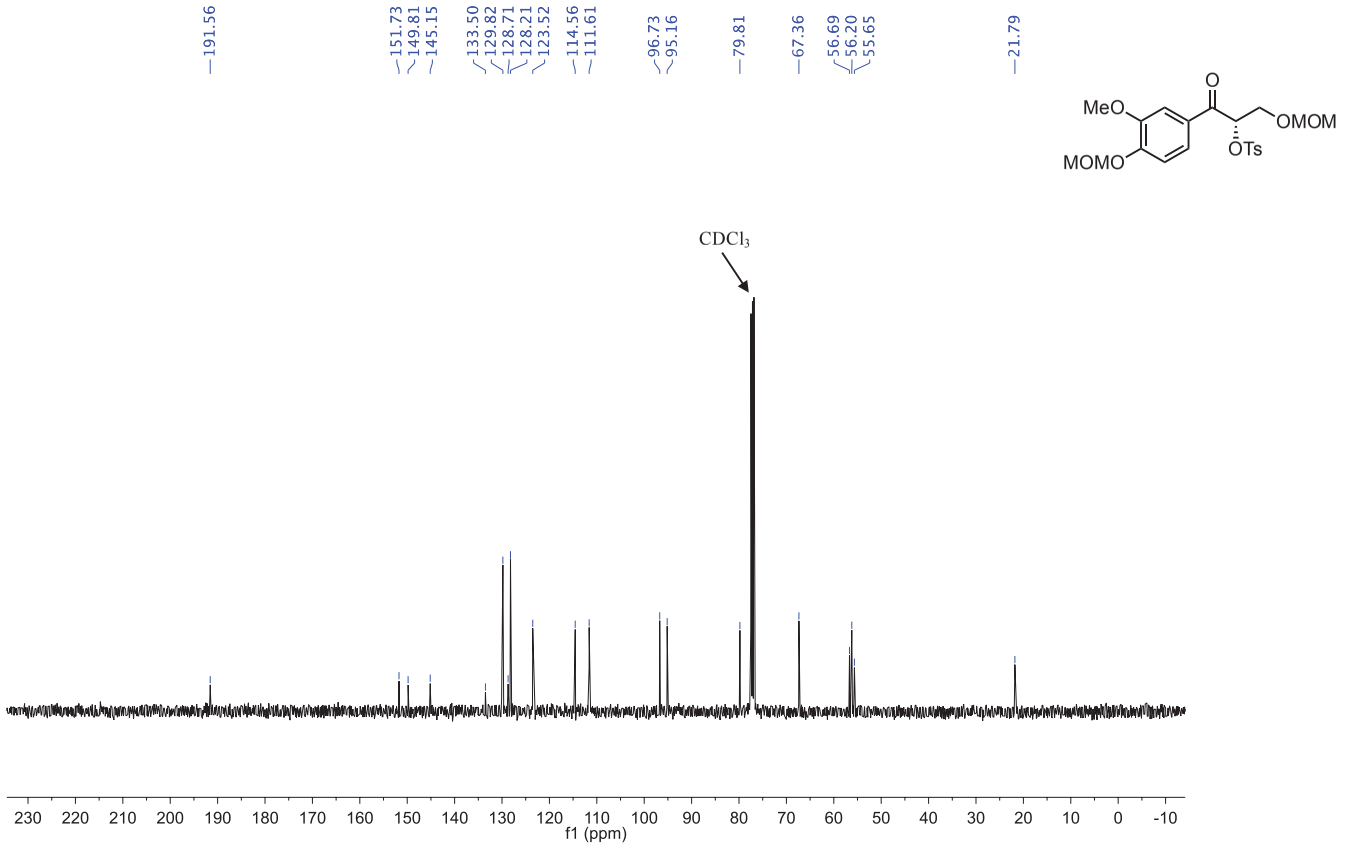


Figure S31. 400 MHz ^{1}H NMR Spectrum of Compound **9** (recorded in $CDCl_3$)

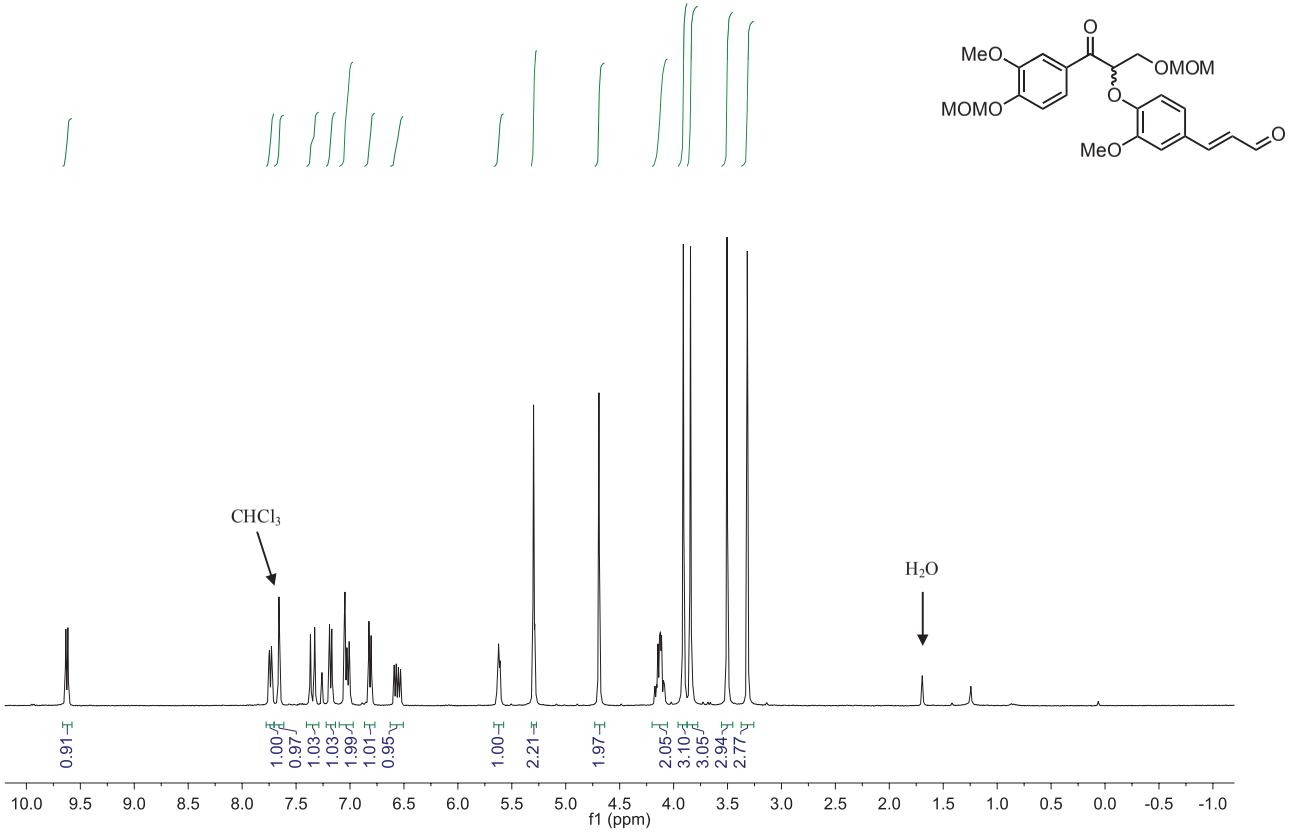


Figure S32. 100 MHz ^{13}C NMR Spectrum of Compound **9** (recorded in $CDCl_3$)

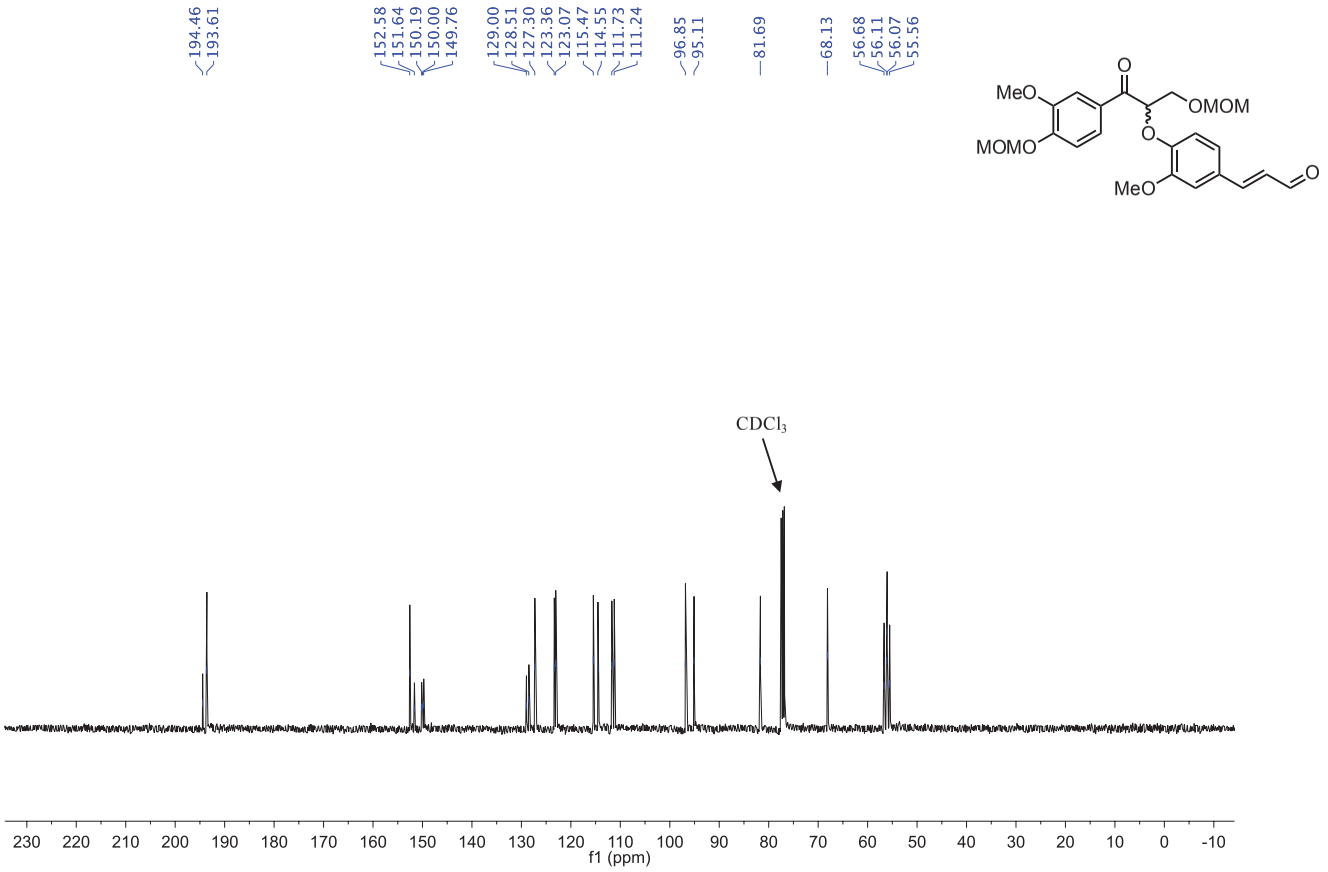


Figure S33. 400 MHz ^{1}H NMR Spectrum of Compound **10** (recorded in $CDCl_3$)

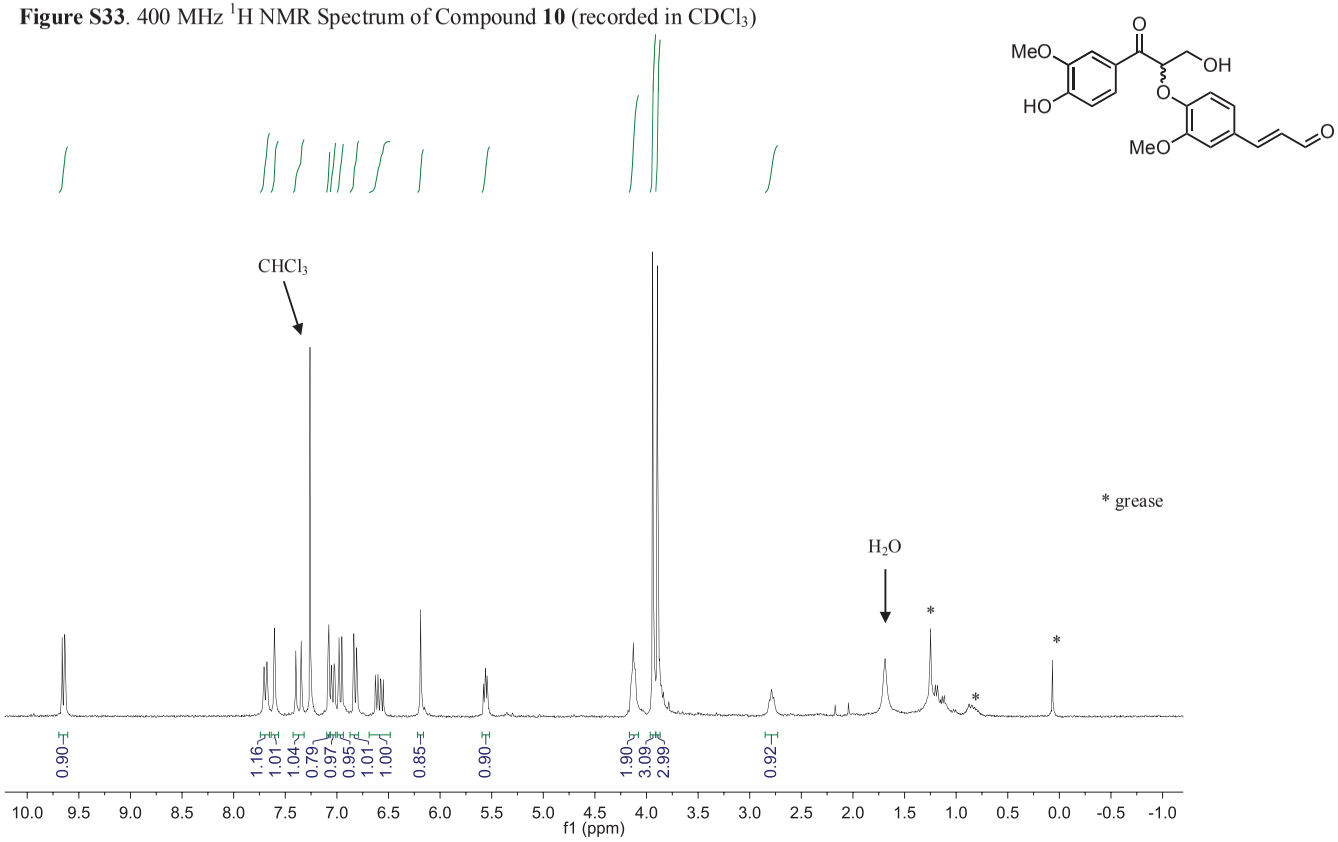


Figure S34. 100 MHz ^{13}C NMR Spectrum of Compound **10** (recorded in $CDCl_3$)

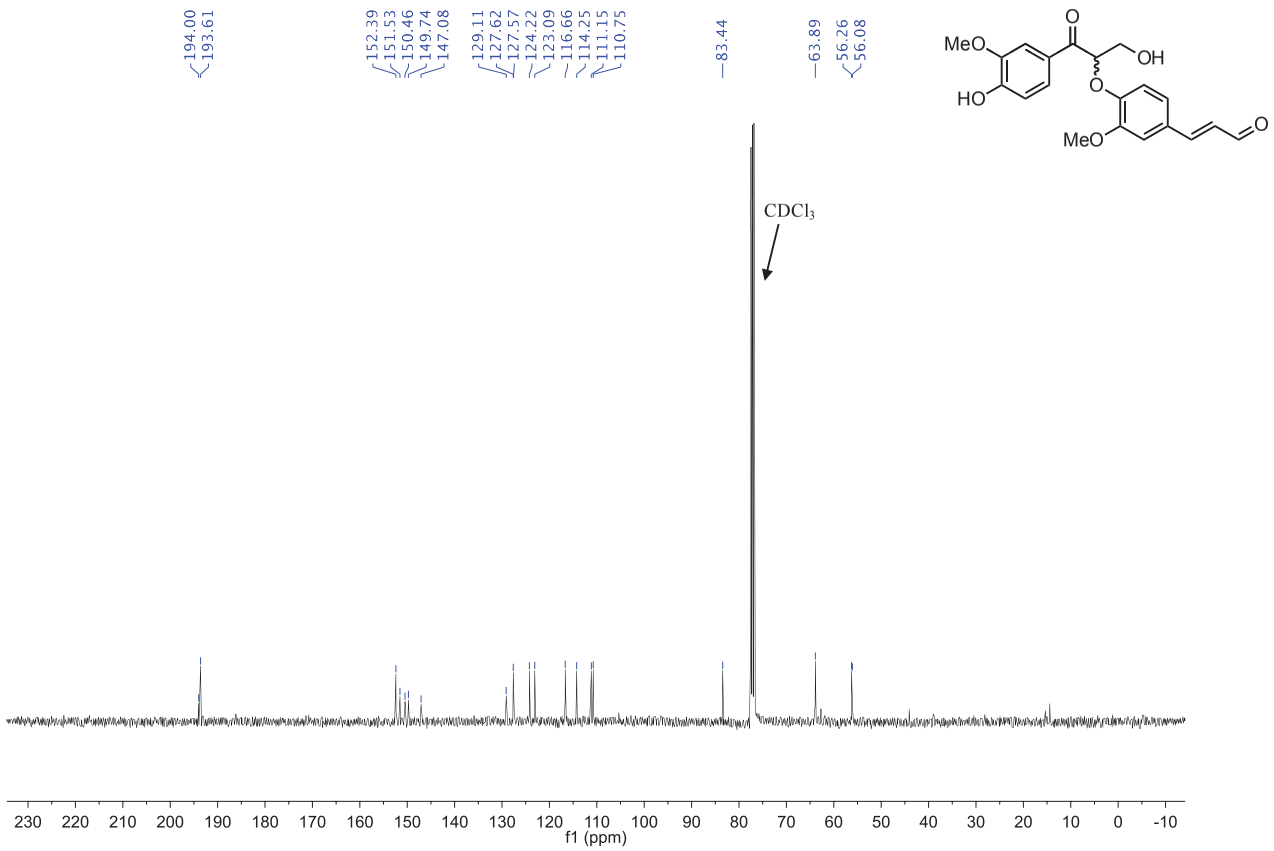


Figure S35. 400 MHz ^{1}H NMR Spectrum of Compound **14** (recorded in $CDCl_3$)

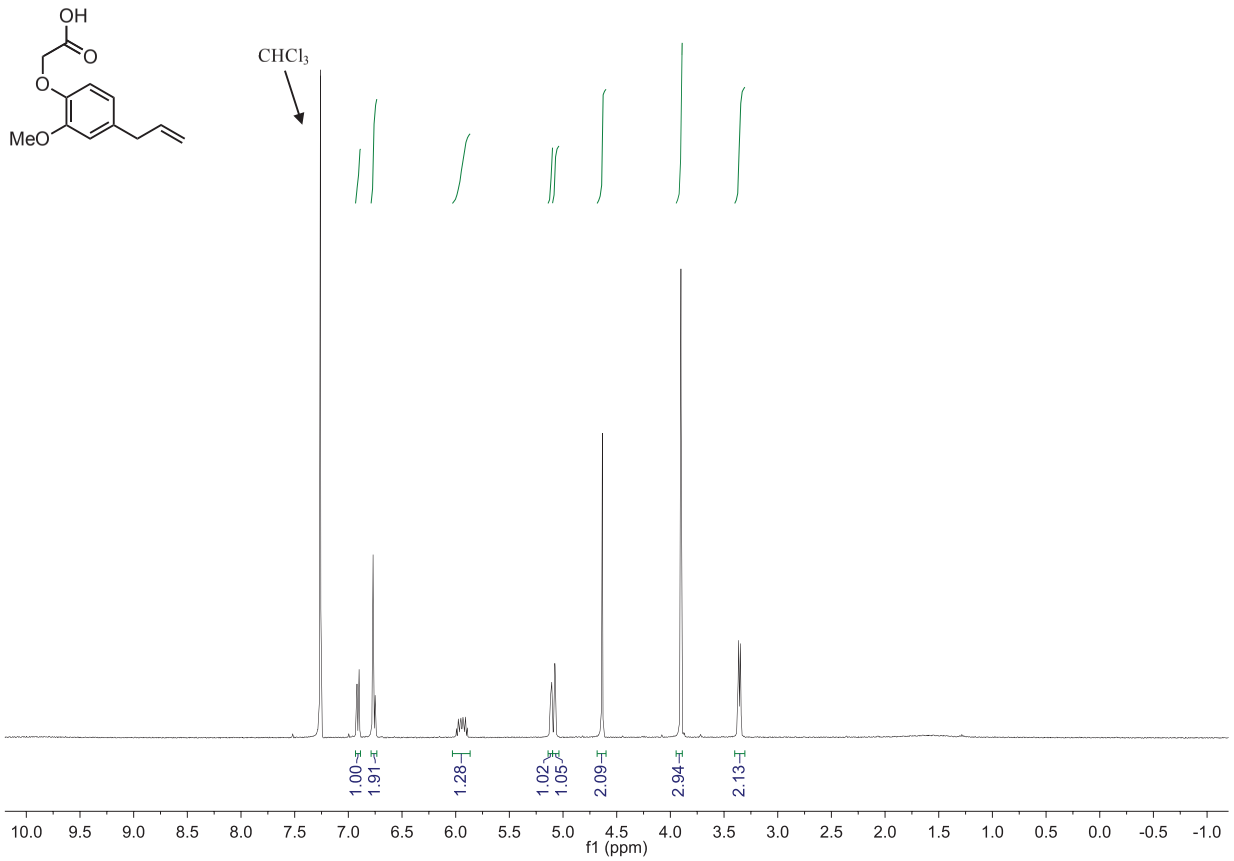


Figure S36. 100 MHz ^{13}C NMR Spectrum of Compound **14** (recorded in $CDCl_3$)

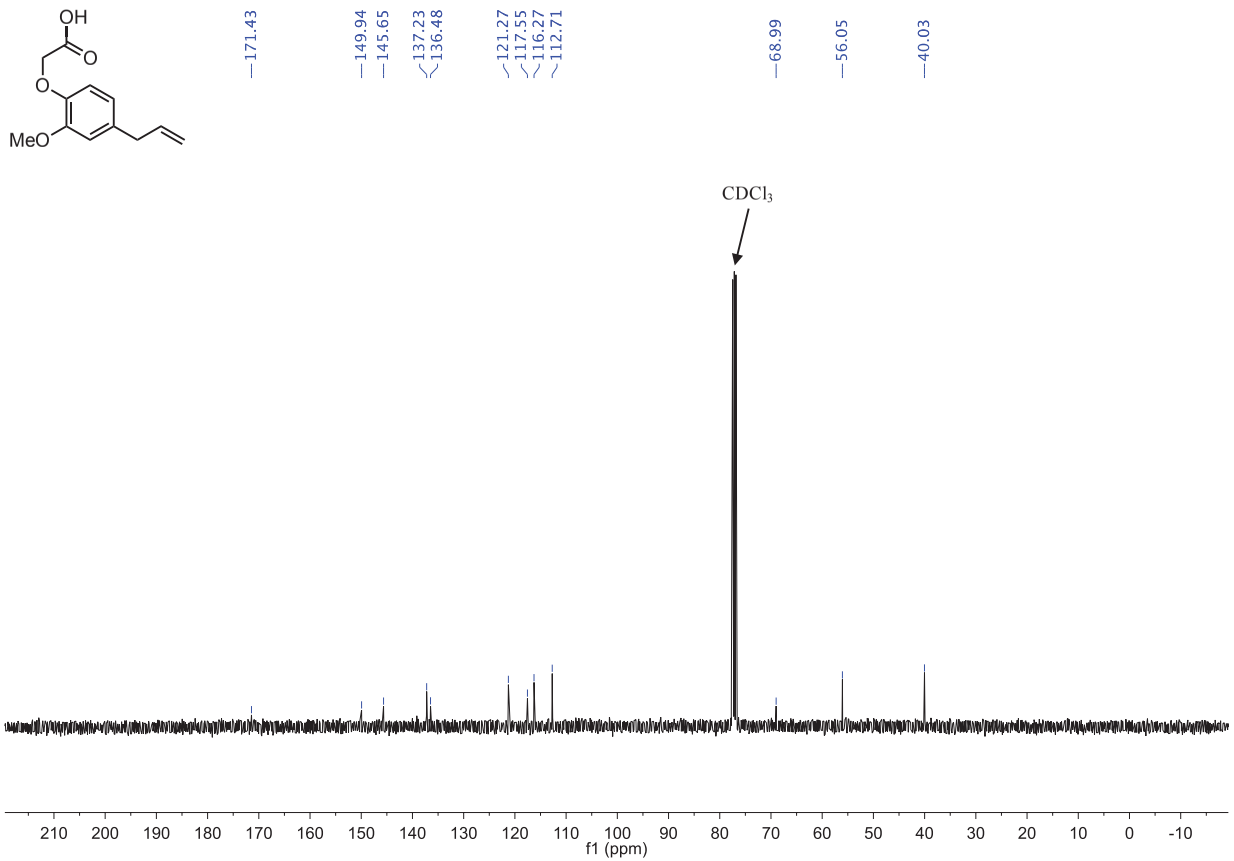


Figure S37. 400 MHz ^{1}H NMR Spectrum of Compound **15** (recorded in $CDCl_3$)

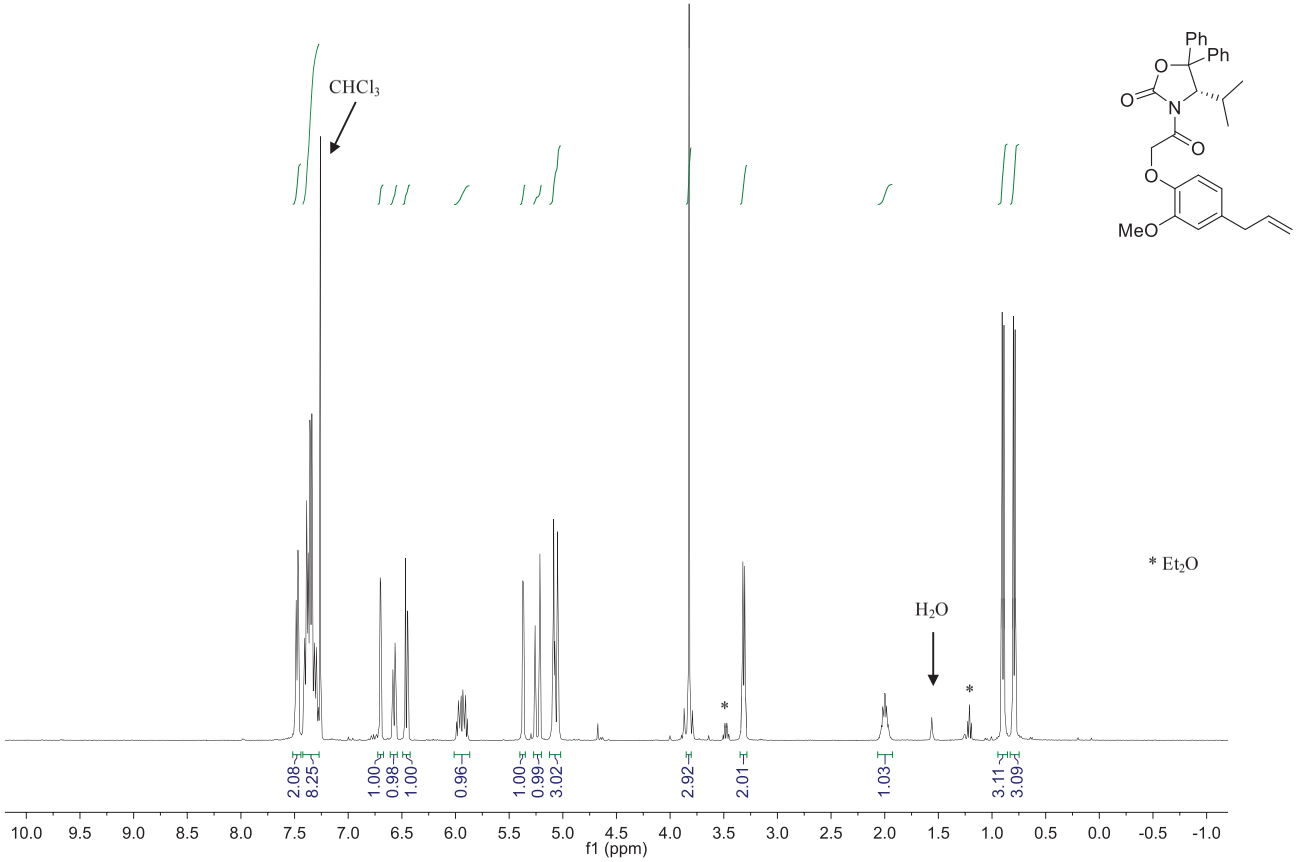


Figure S38. 100 MHz ^{13}C NMR Spectrum of Compound **15** (recorded in $CDCl_3$)

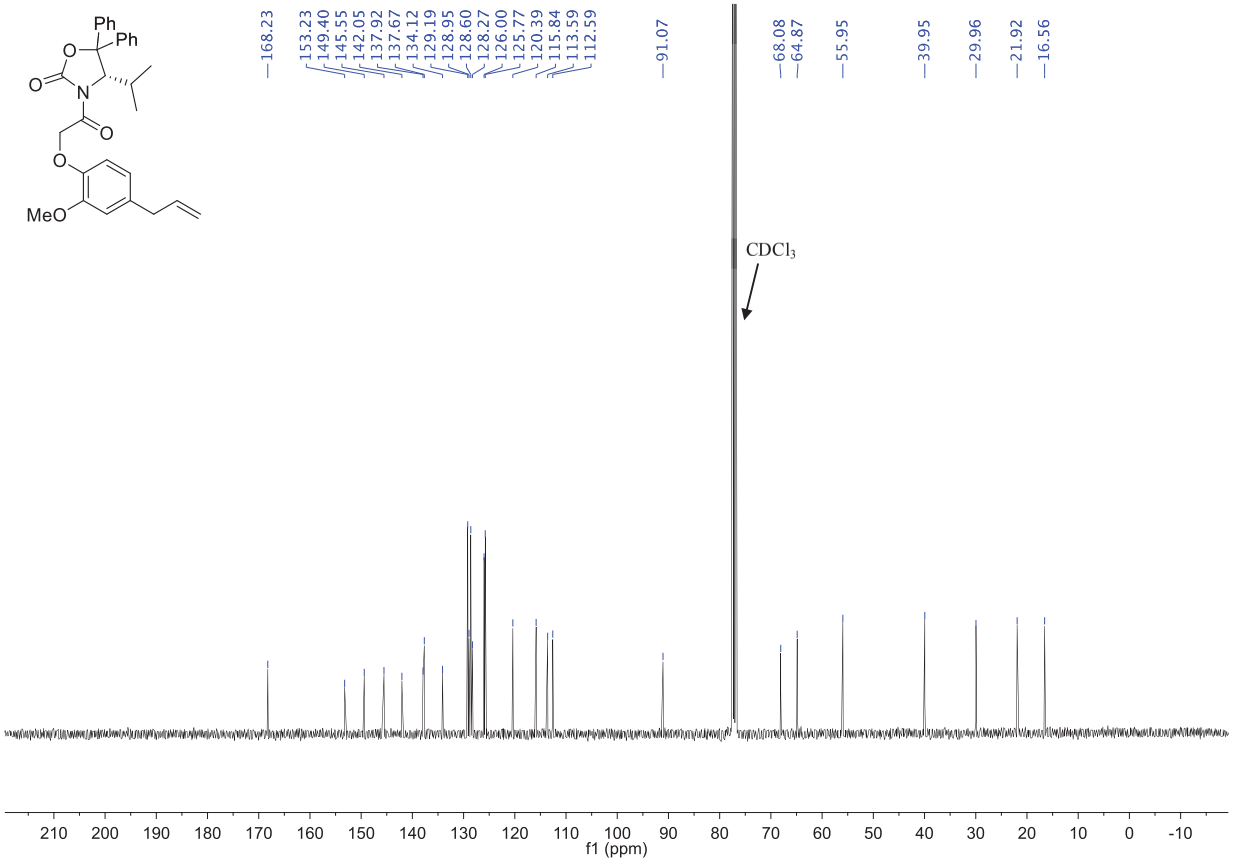


Figure S39. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**15** (recorded in $CDCl_3$)

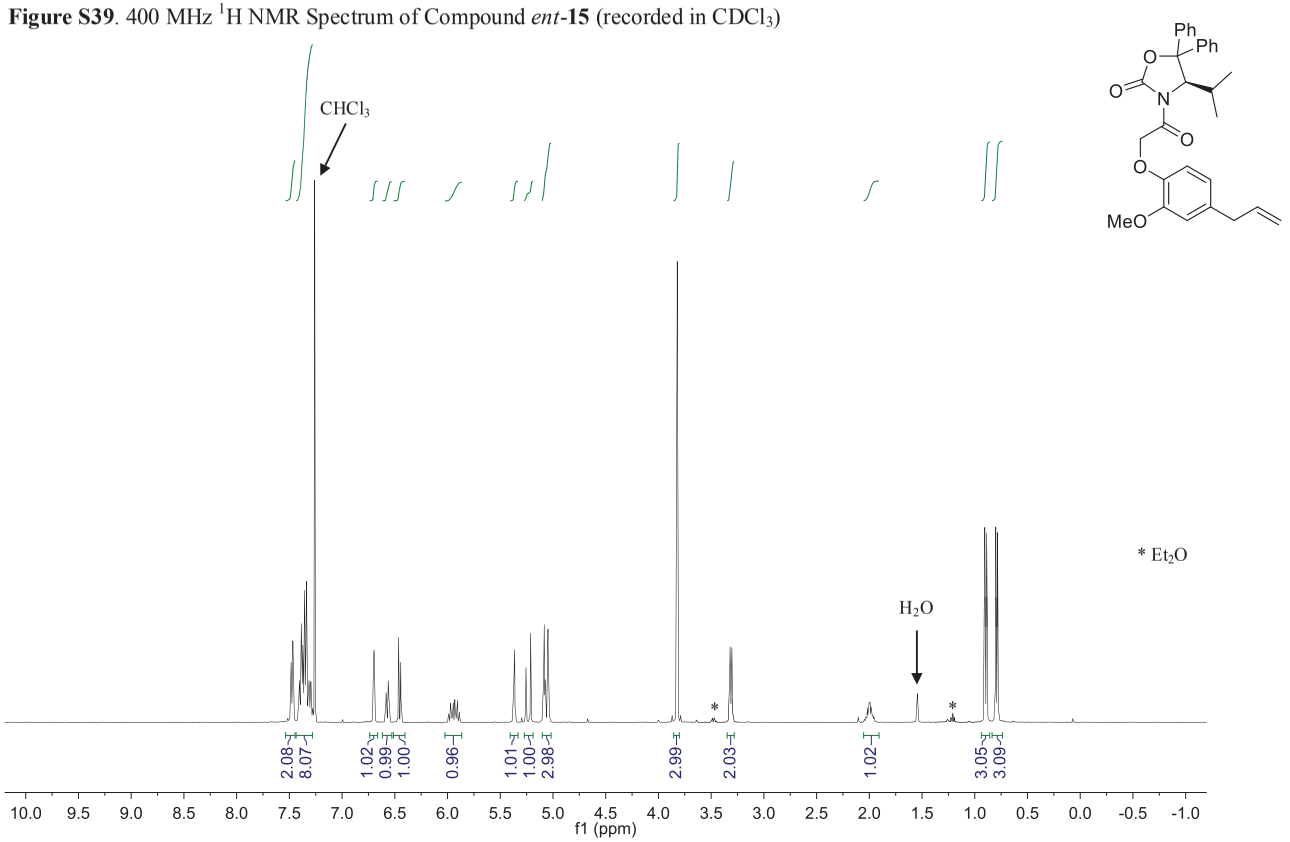


Figure S40. 400 MHz ^{1}H NMR Spectrum of Aldol Precursor to Compound **17** (recorded in $CDCl_3$)

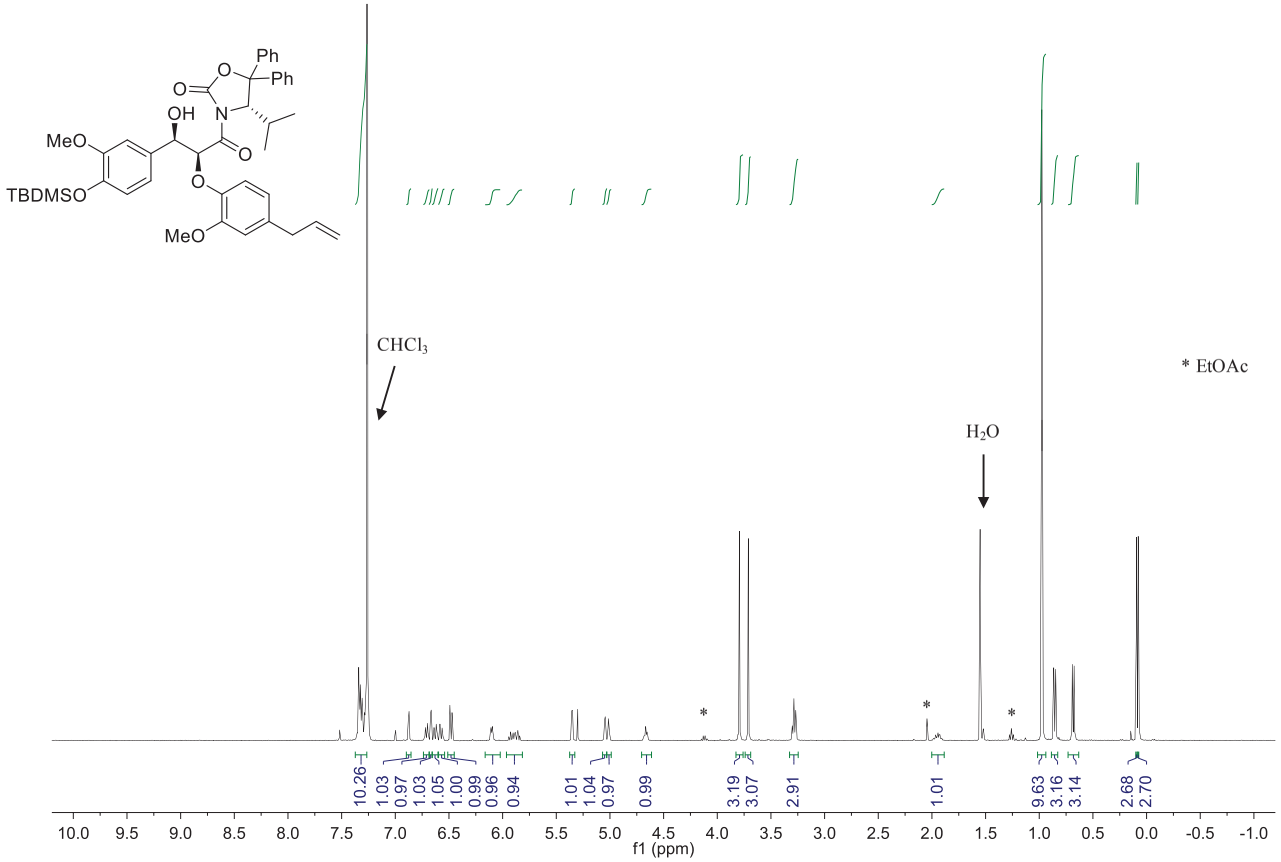


Figure S41. 100 MHz ^{13}C NMR Spectrum of Aldol Precursor to Compound **17** (recorded in $CDCl_3$)

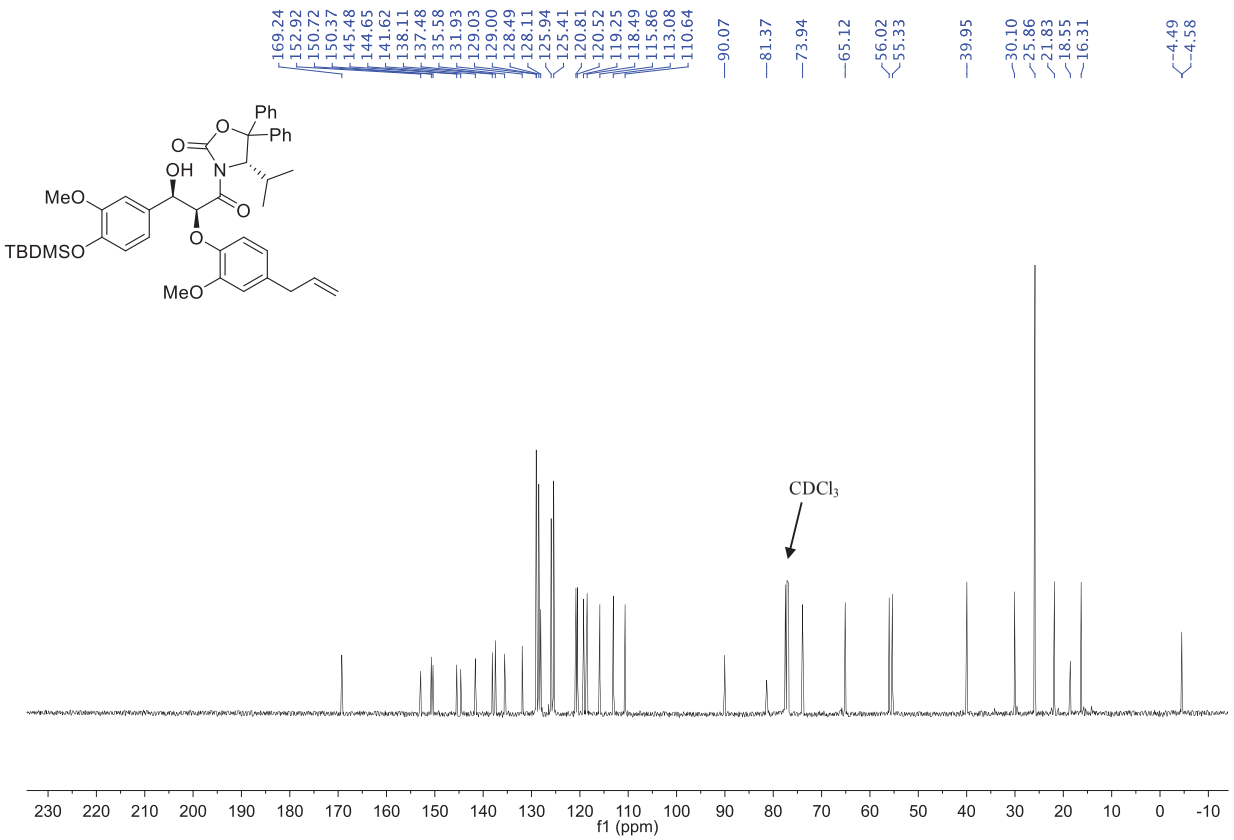


Figure S42. 400 MHz ^{1}H NMR Spectrum of Aldol Precursor to Compound *ent*-**17** (recorded in $CDCl_3$)

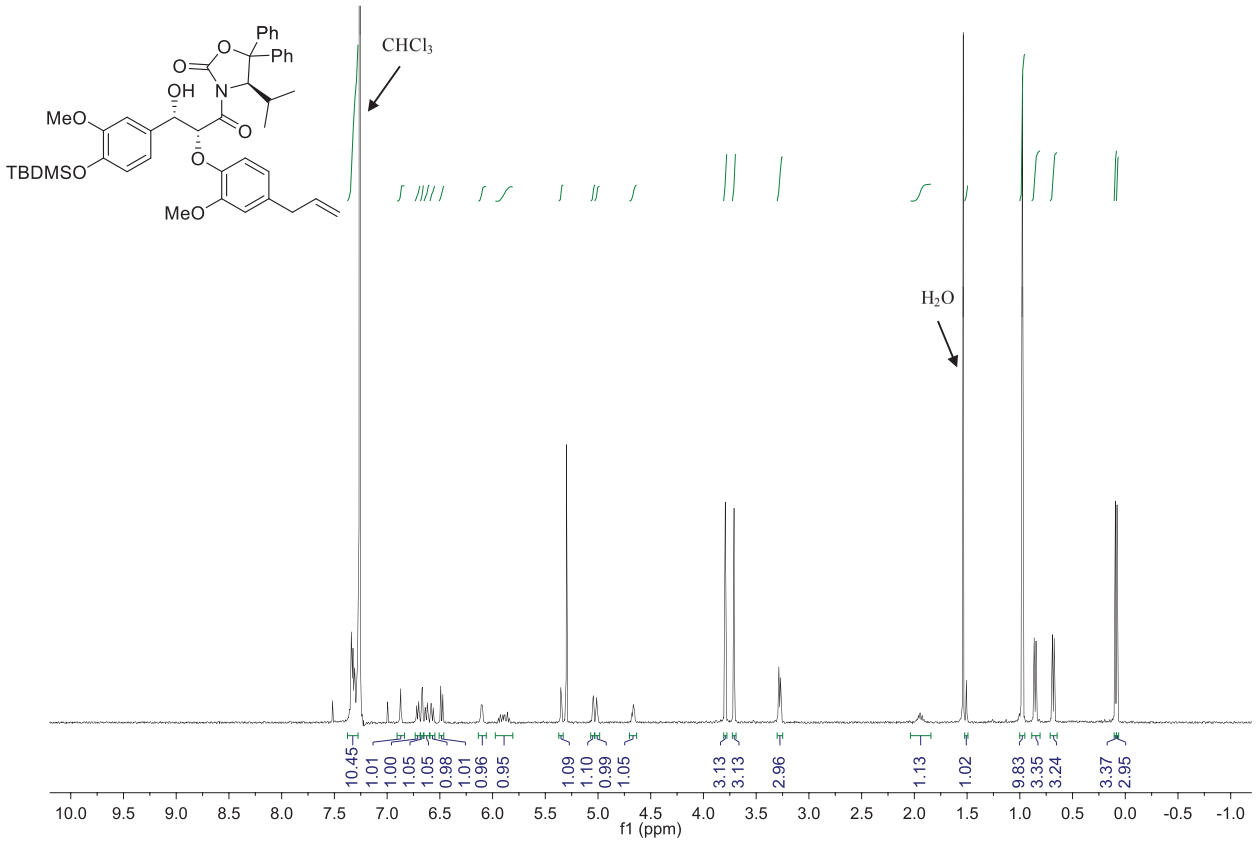


Figure S43. 400 MHz ^{1}H NMR Spectrum of Compound **17** (recorded in $CDCl_3$)

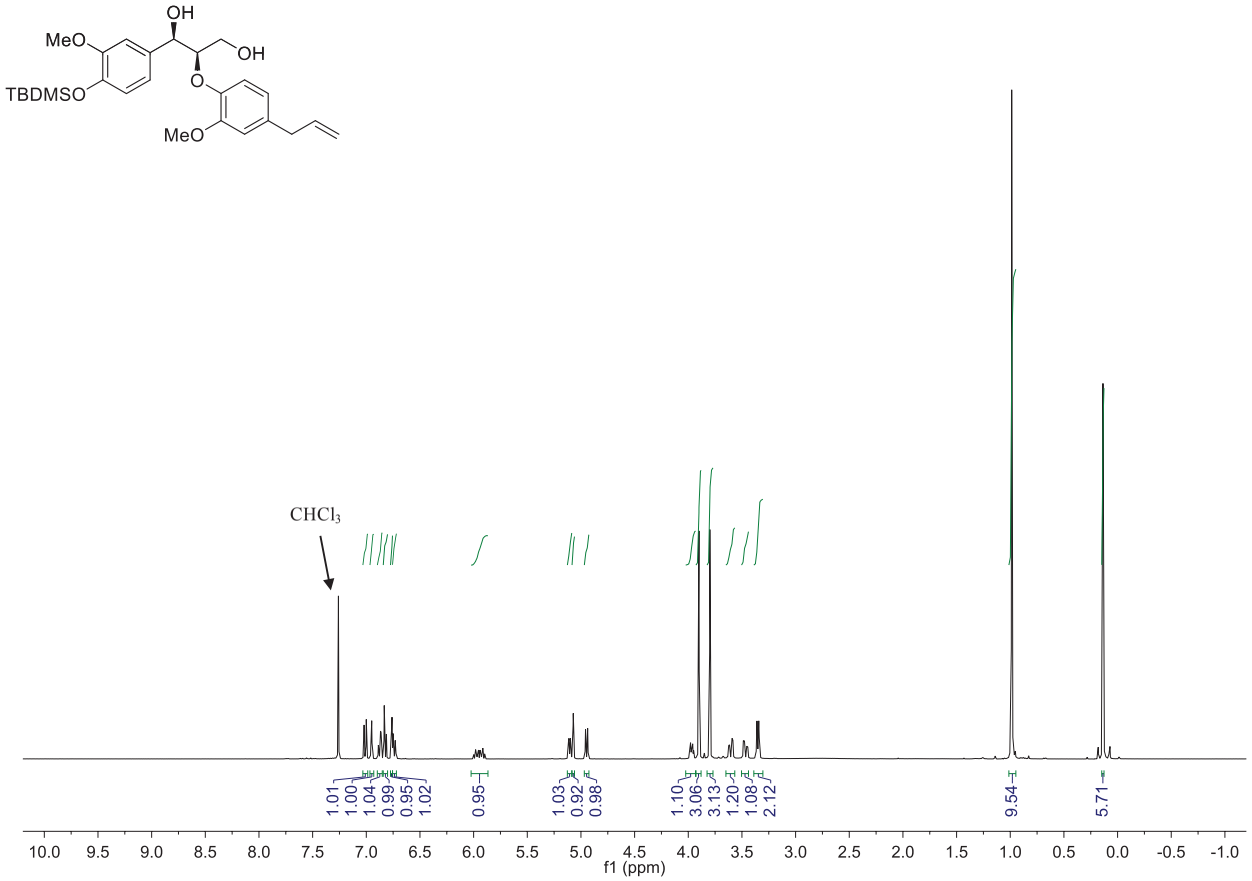


Figure S44. 100 MHz ^{13}C NMR Spectrum of Compound **17** (recorded in $CDCl_3$)

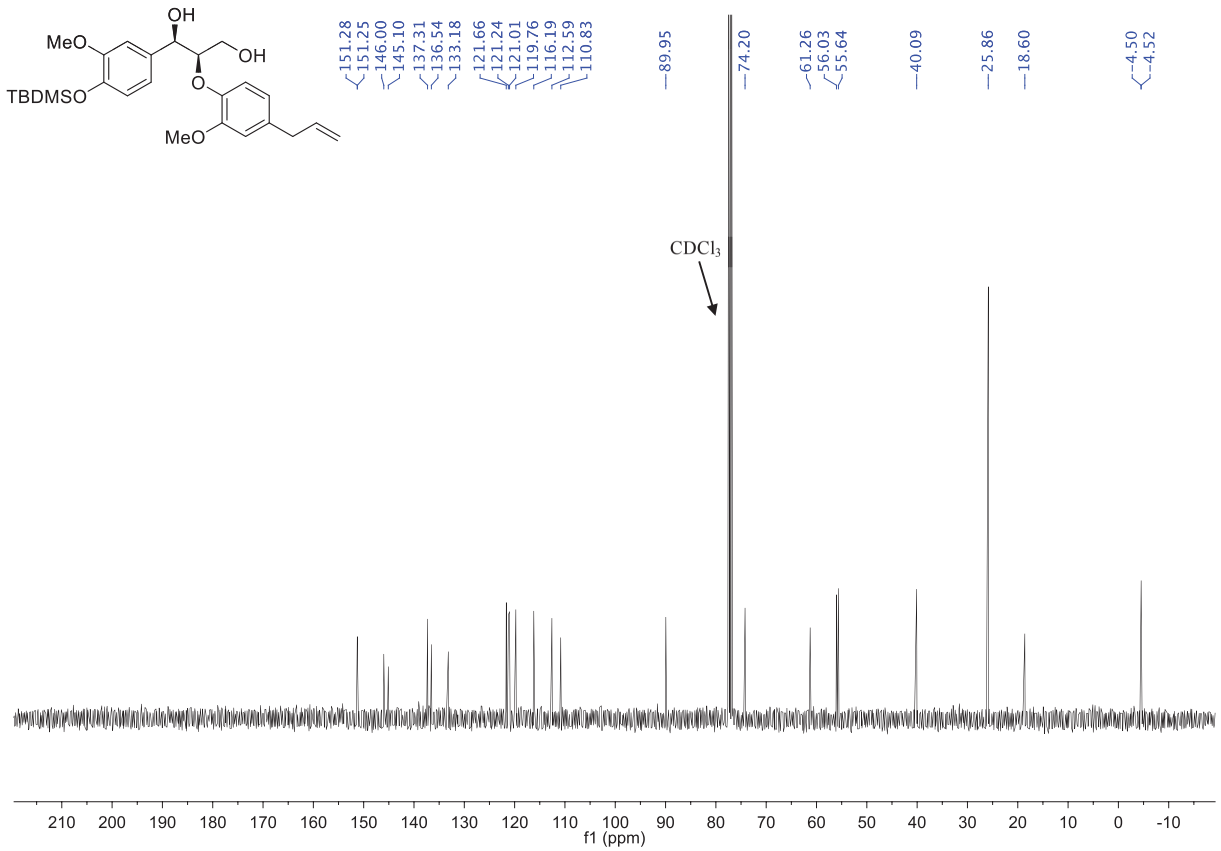


Figure S45. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**17** (recorded in $CDCl_3$)

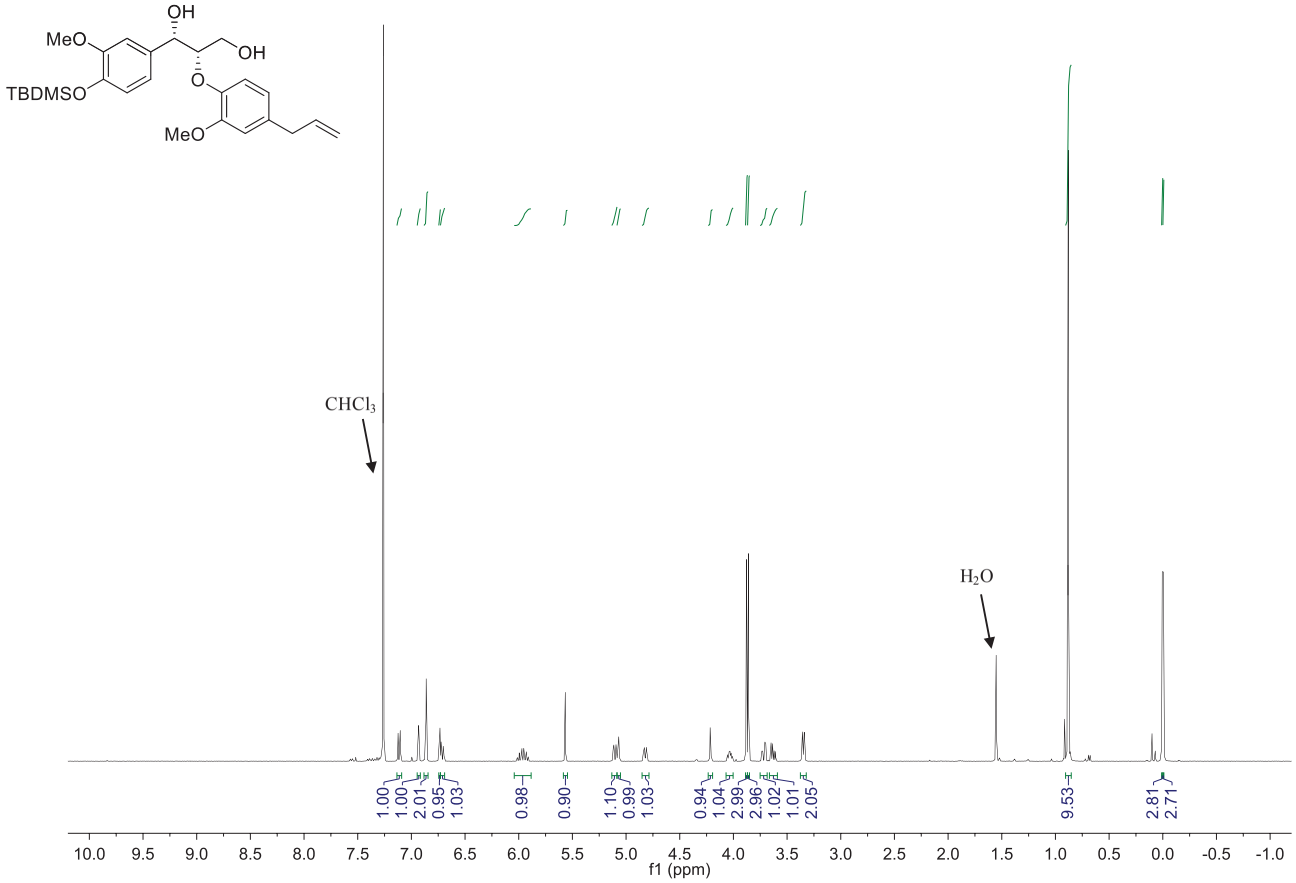


Figure S46. 400 MHz ^{1}H NMR Spectrum of Compound **18** (recorded in $CDCl_3$)

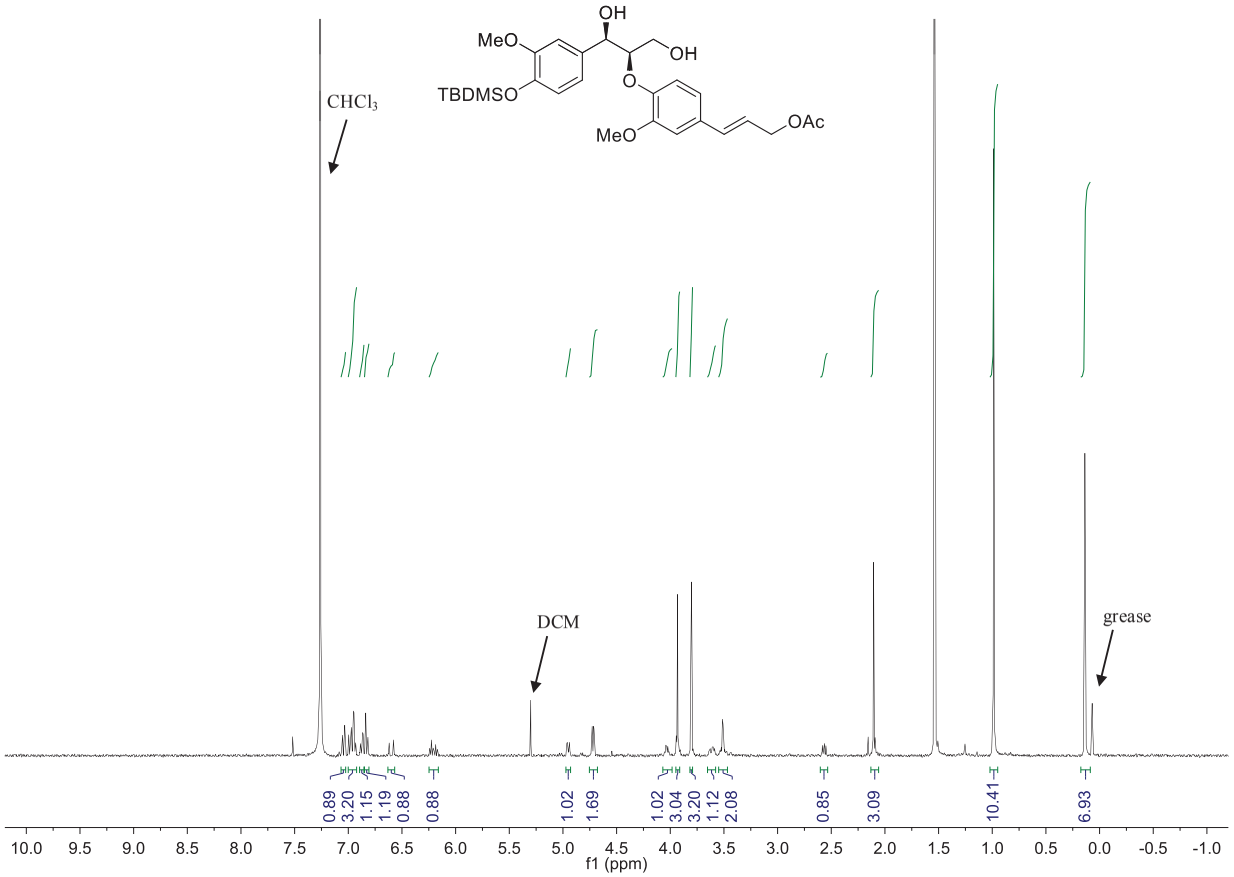


Figure S47. 100 MHz ^{13}C NMR Spectrum of Compound **18** (recorded in $CDCl_3$)

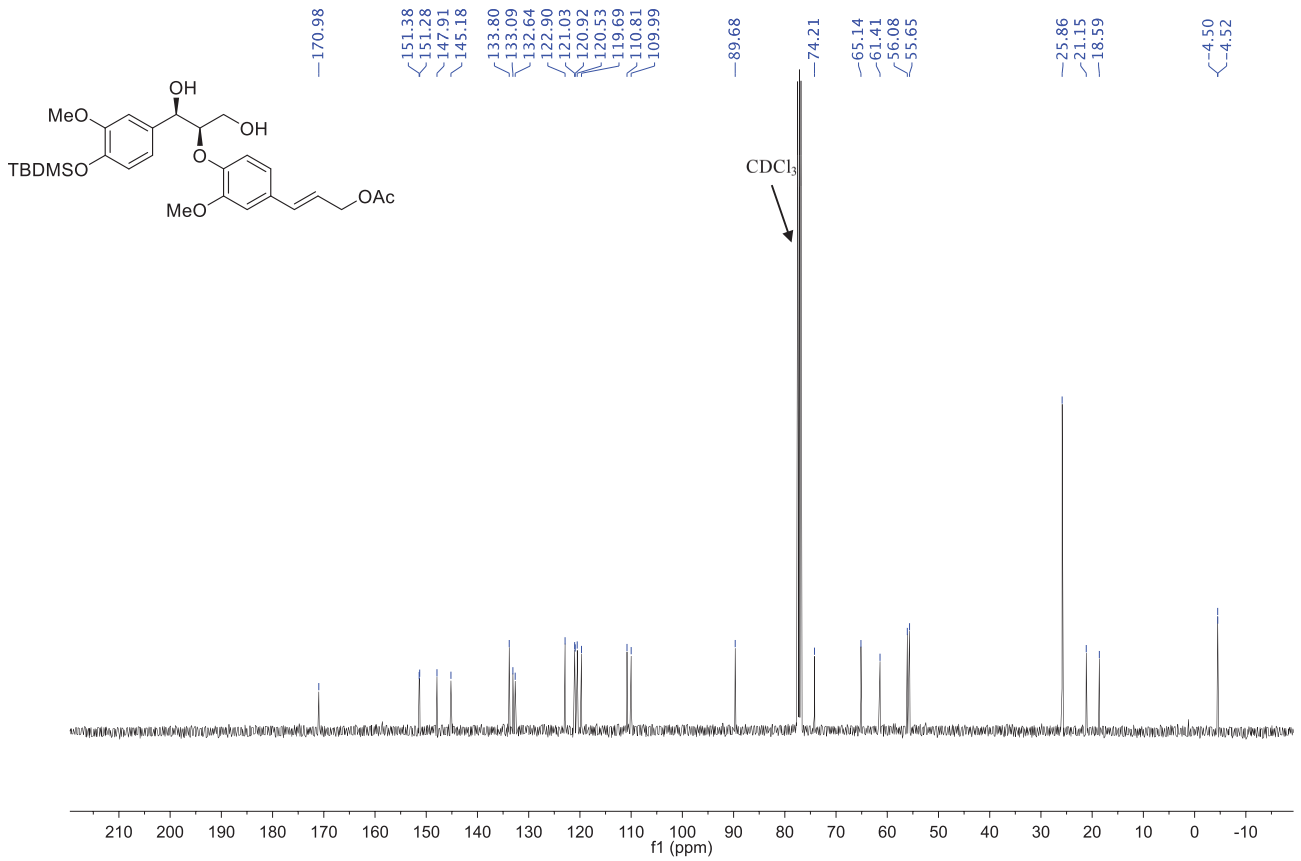


Figure S48. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**18** (recorded in $CDCl_3$)

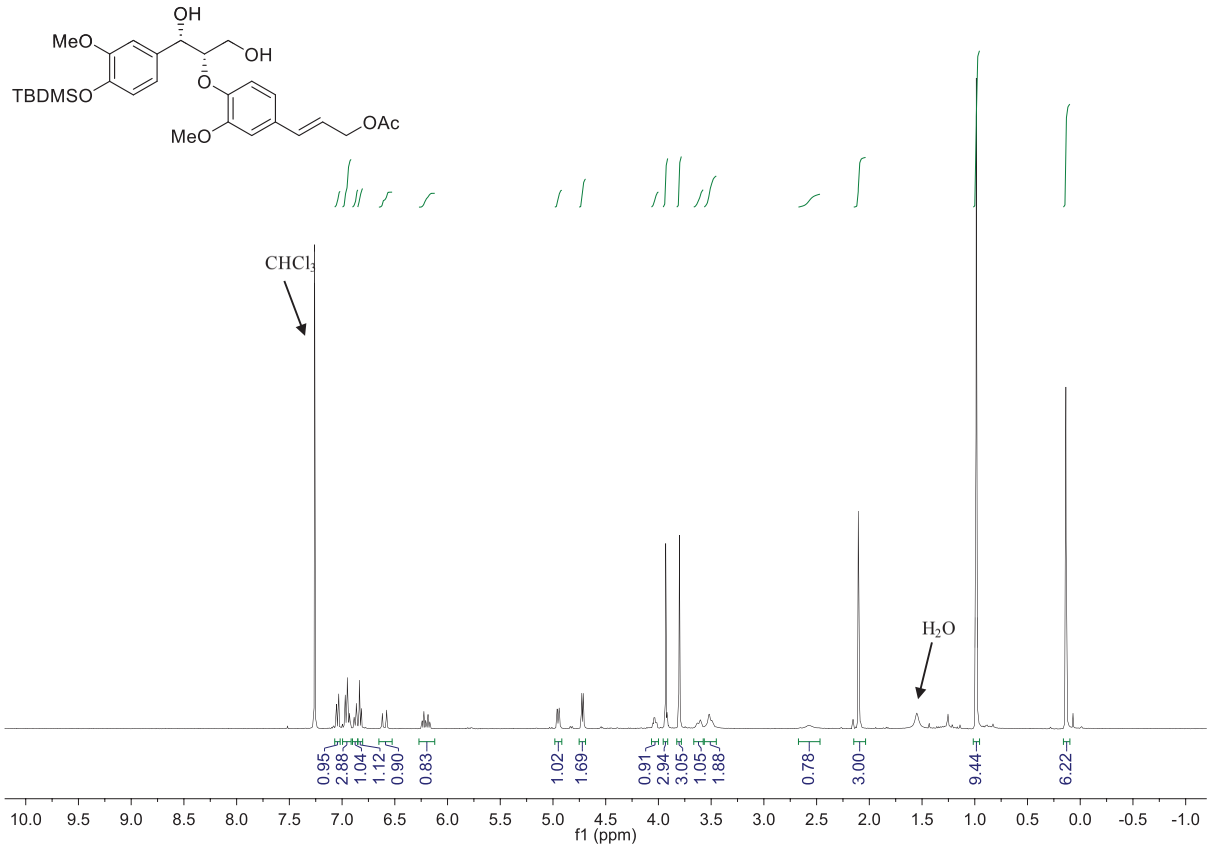


Figure S49. 400 MHz ^{1}H NMR Spectrum of Compound **19** (recorded in $CDCl_3$)

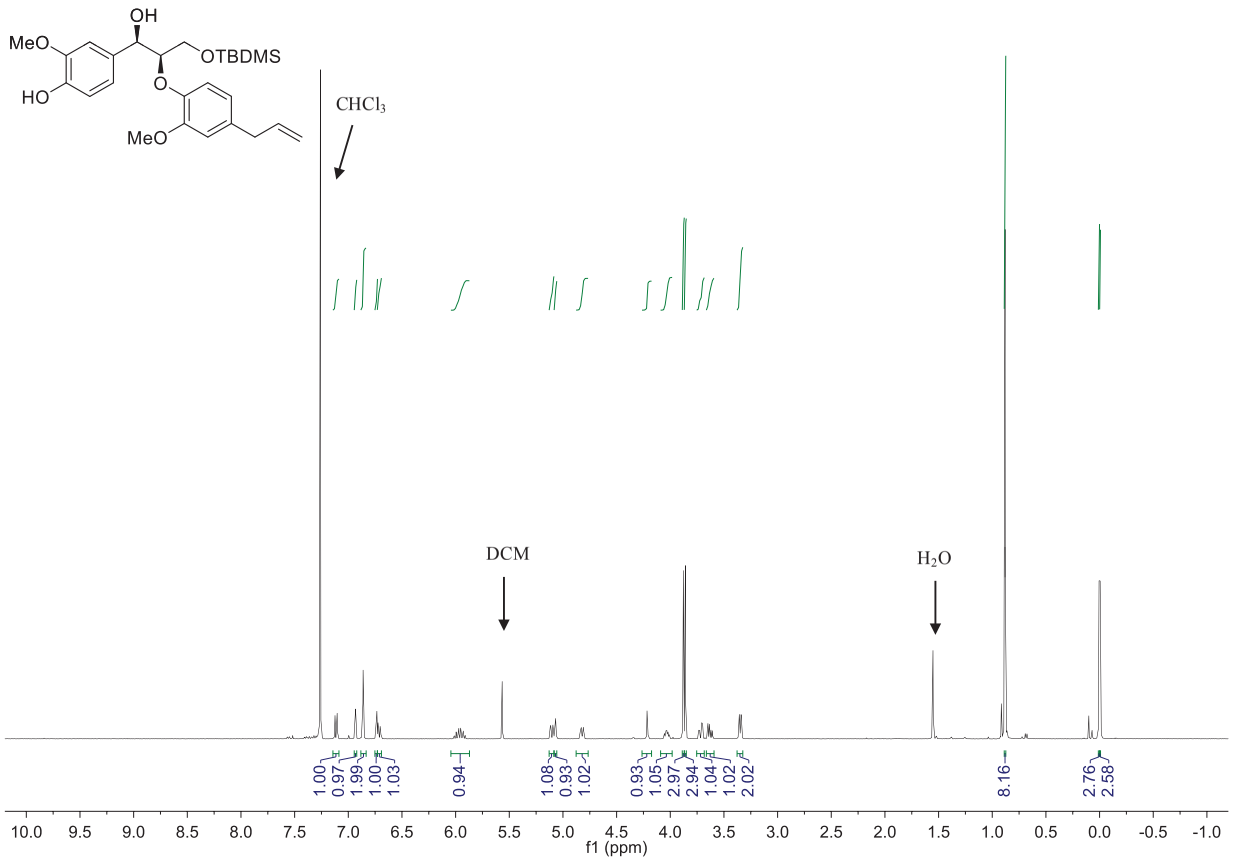


Figure S50. 100 MHz ^{13}C NMR Spectrum of Compound **19** (recorded in $CDCl_3$)

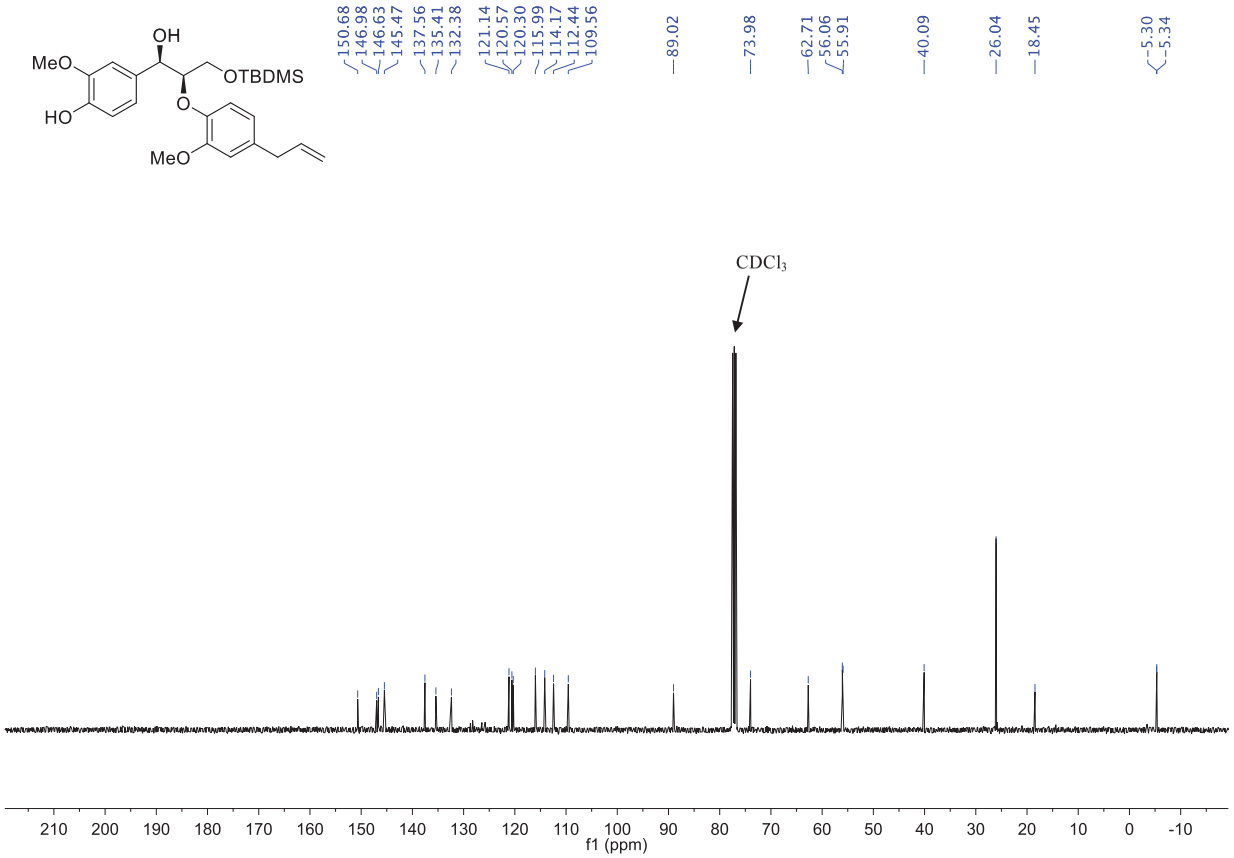


Figure S51. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**19** (recorded in $CDCl_3$)

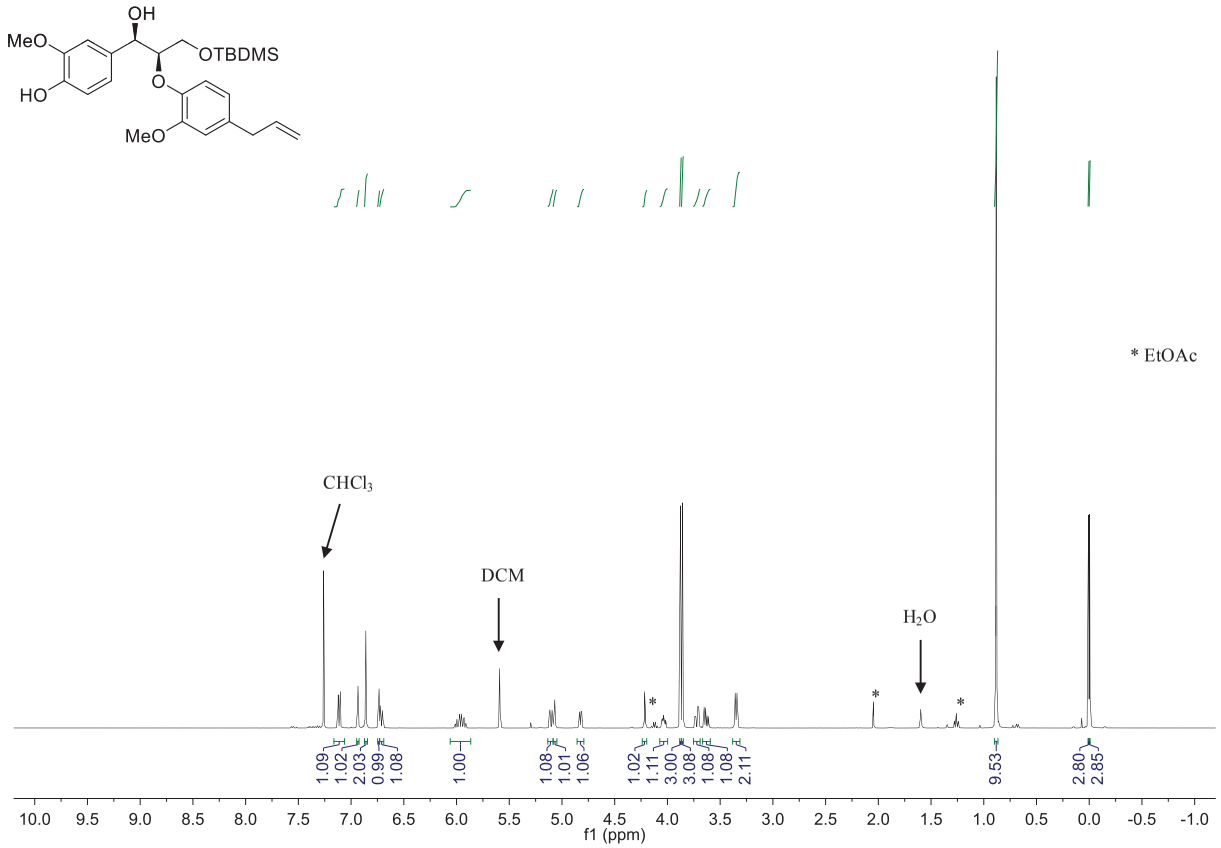


Figure S52. 400 MHz ^{1}H NMR Spectrum of Compound **20** (recorded in $CDCl_3$)

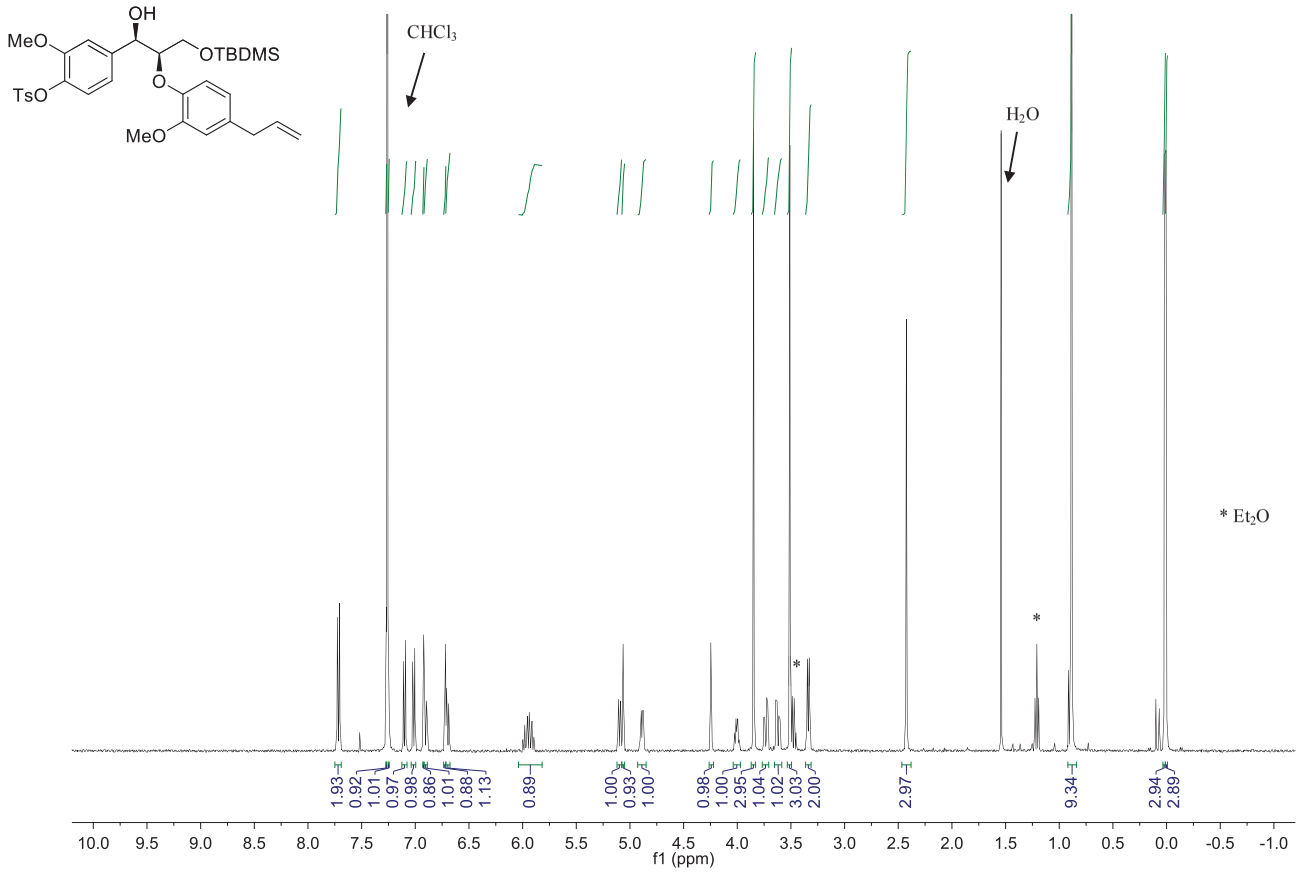


Figure S53. 100 MHz ^{13}C NMR Spectrum of Compound **20** (recorded in $CDCl_3$)

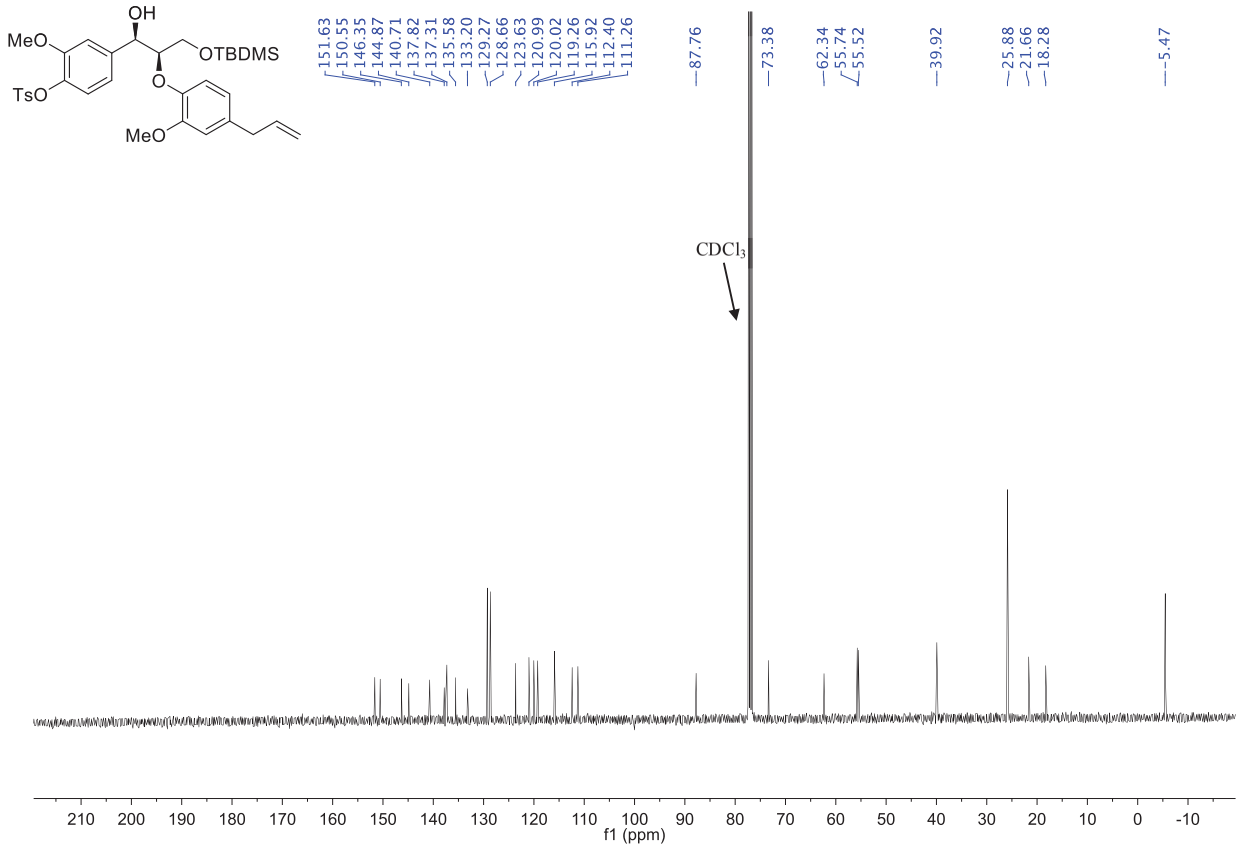


Figure S54. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**20** (recorded in $CDCl_3$)

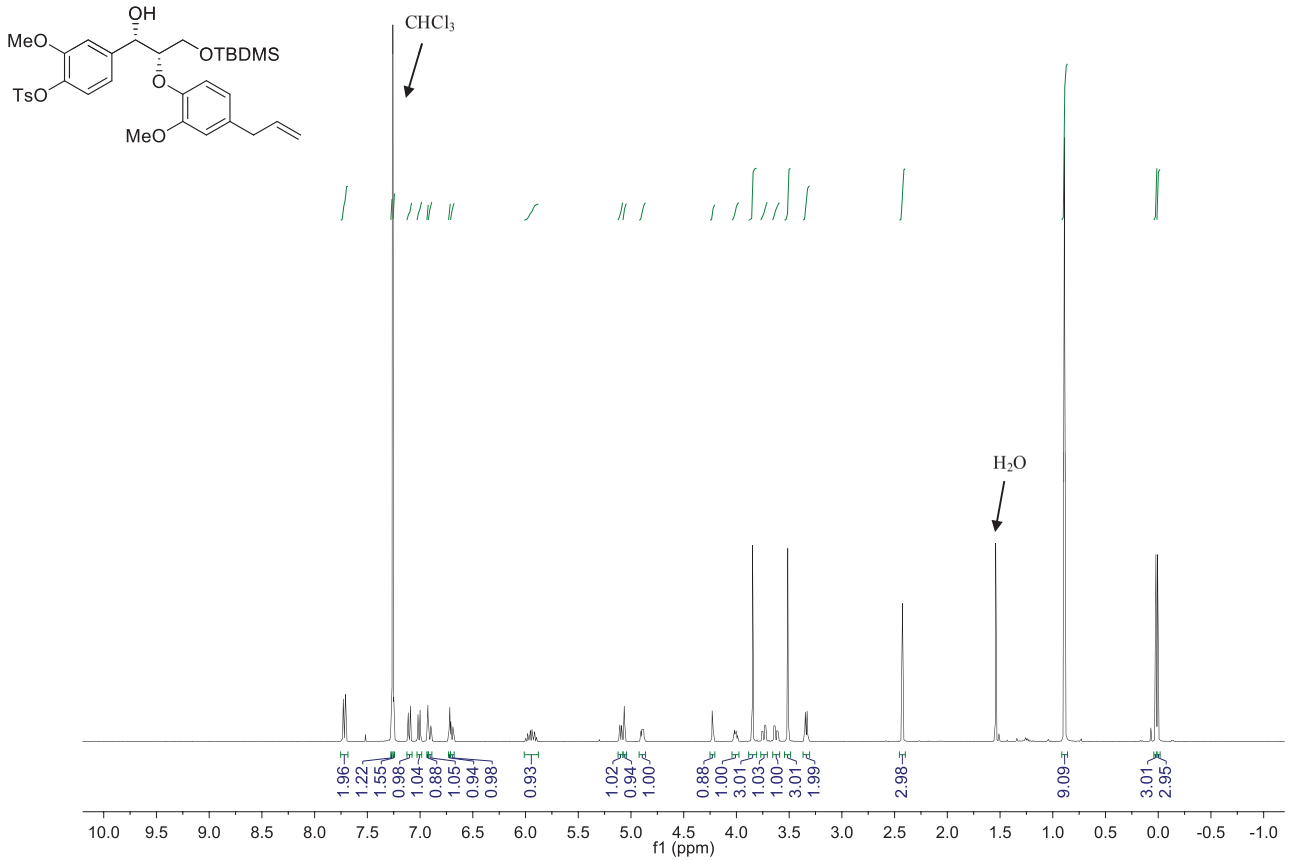


Figure S55. 400 MHz ^{1}H NMR Spectrum of Compound **21** (recorded in $CDCl_3$)

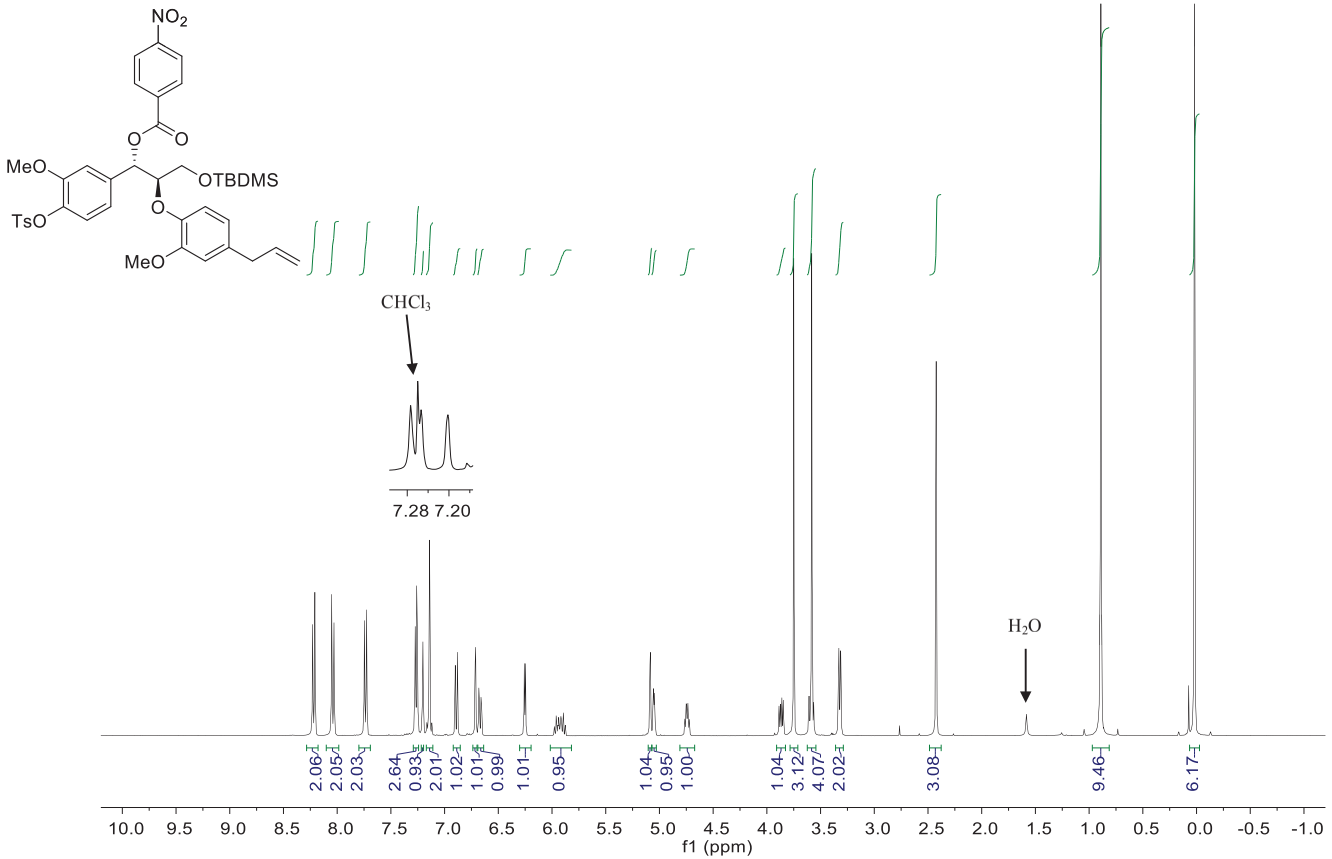


Figure S56. 100 MHz ^{13}C NMR Spectrum of Compound **21** (recorded in $CDCl_3$)

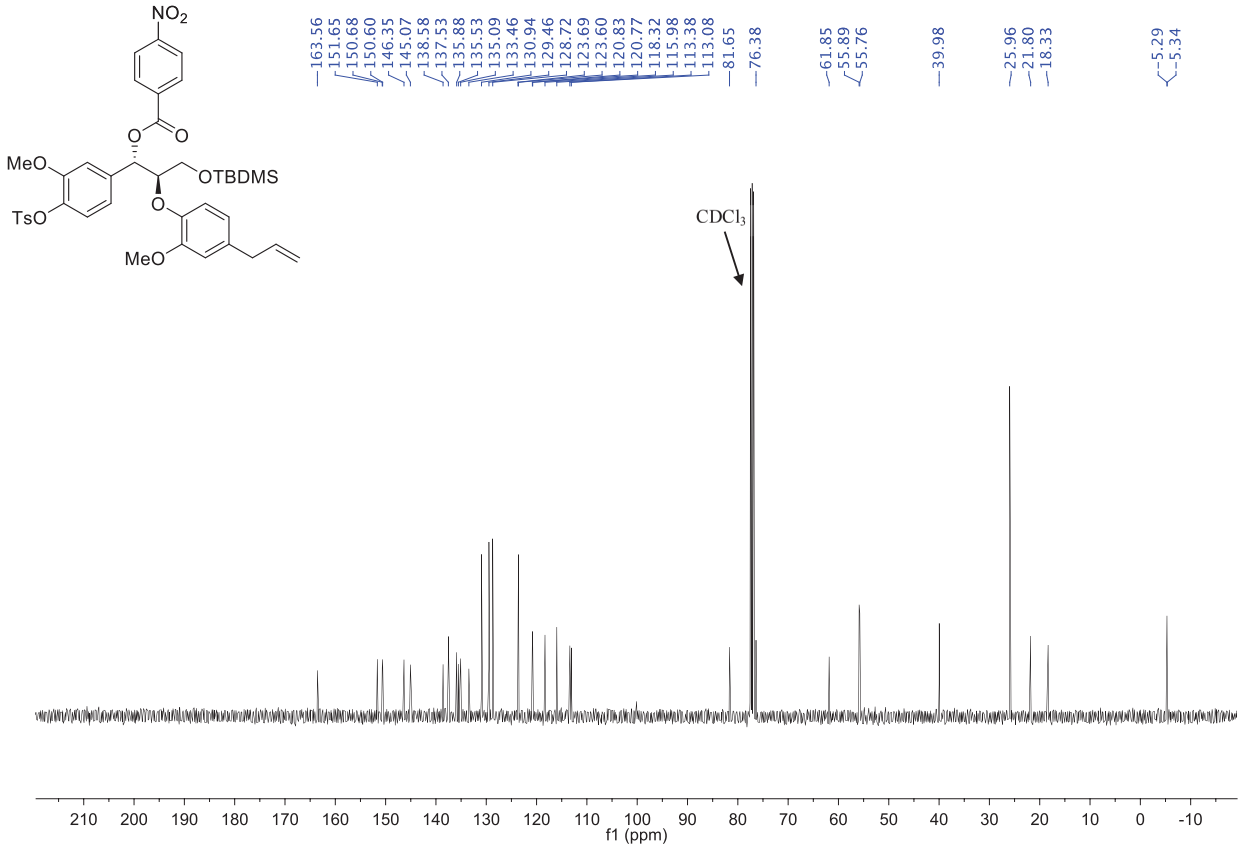


Figure S57. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**21** (recorded in $CDCl_3$)

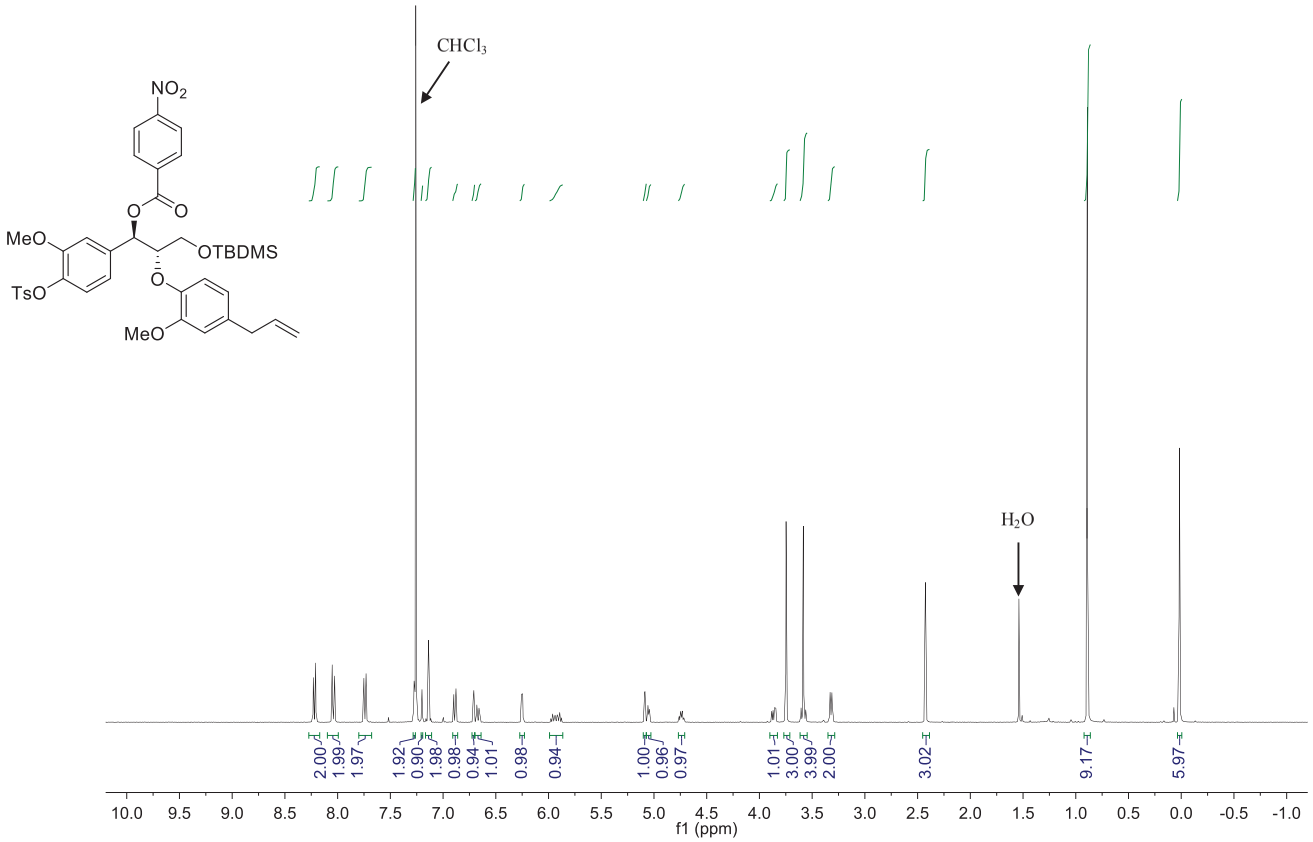


Figure S58. 400 MHz ^{1}H NMR Spectrum of Compound **22** (recorded in $CDCl_3$)

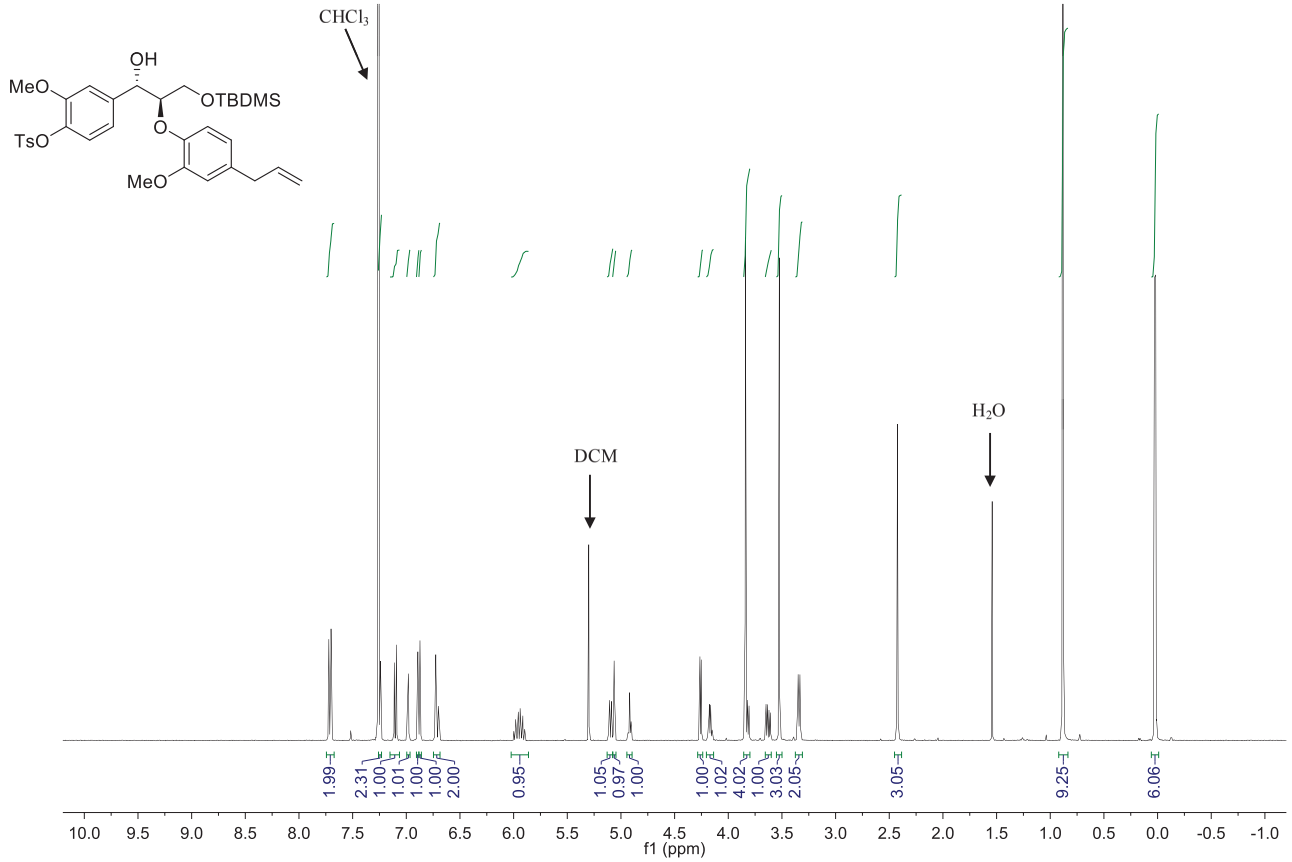


Figure S59. 100 MHz ^{13}C NMR Spectrum of Compound **22** (recorded in $CDCl_3$)

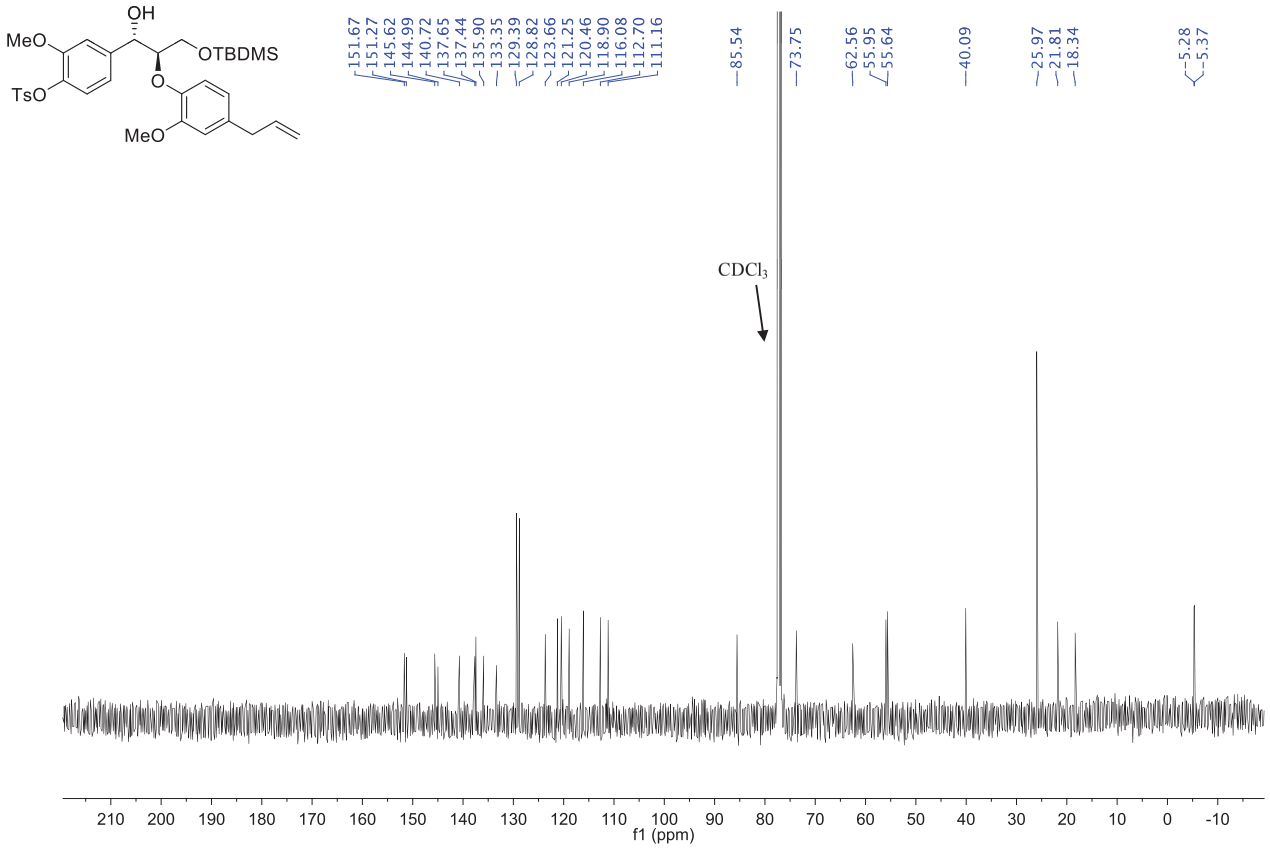


Figure S60. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**22** (recorded in $CDCl_3$)

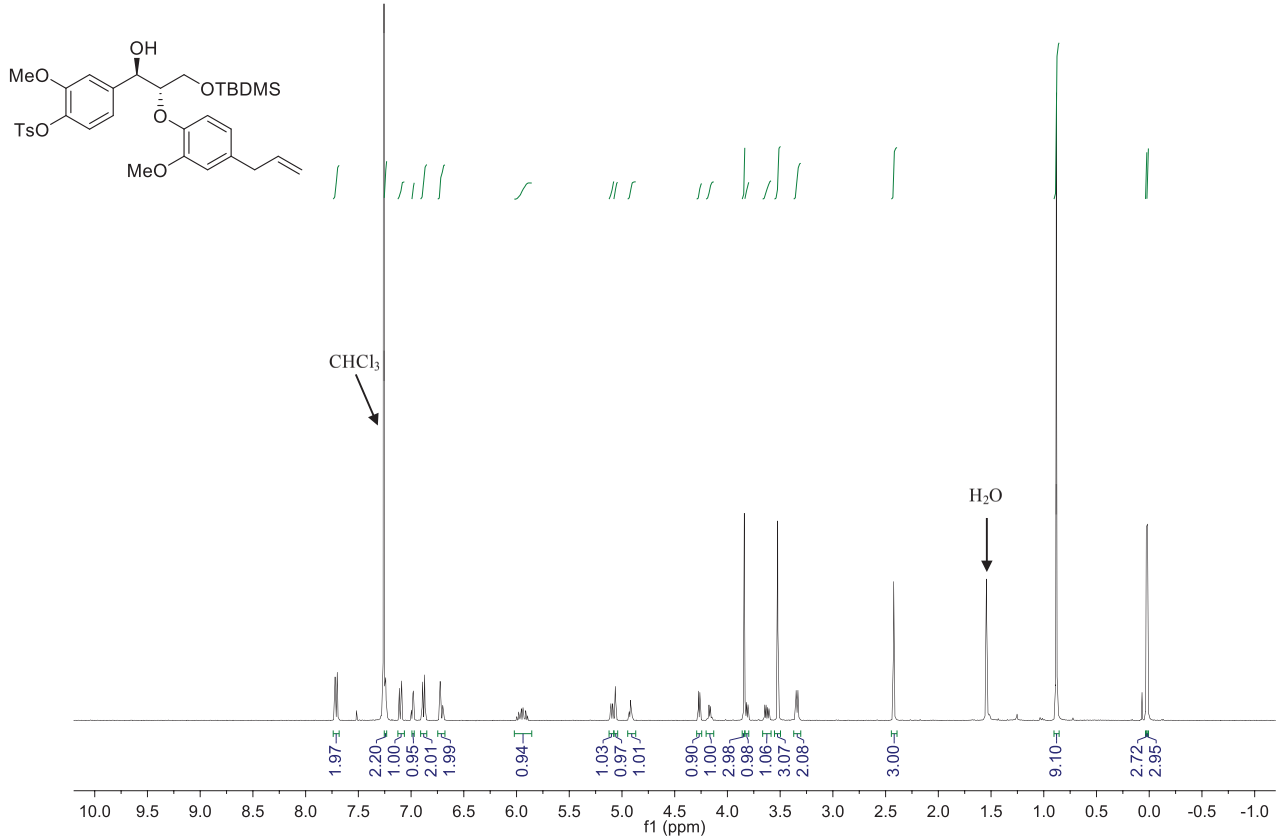


Figure S61. 400 MHz ^{1}H NMR Spectrum of Compound **23** (recorded in $CDCl_3$)

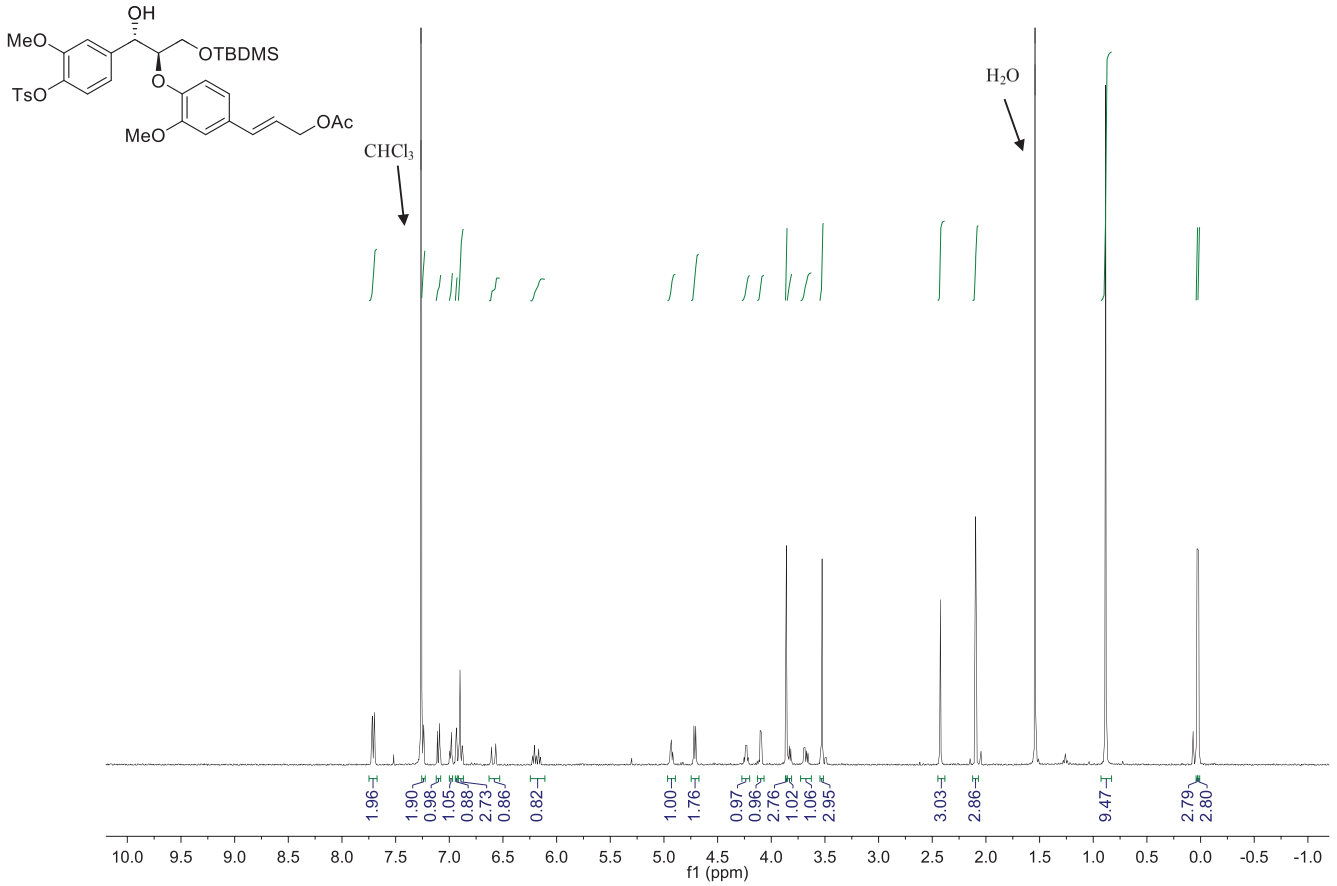


Figure S62. 100 MHz ^{13}C NMR Spectrum of Compound **23** (recorded in $CDCl_3$)

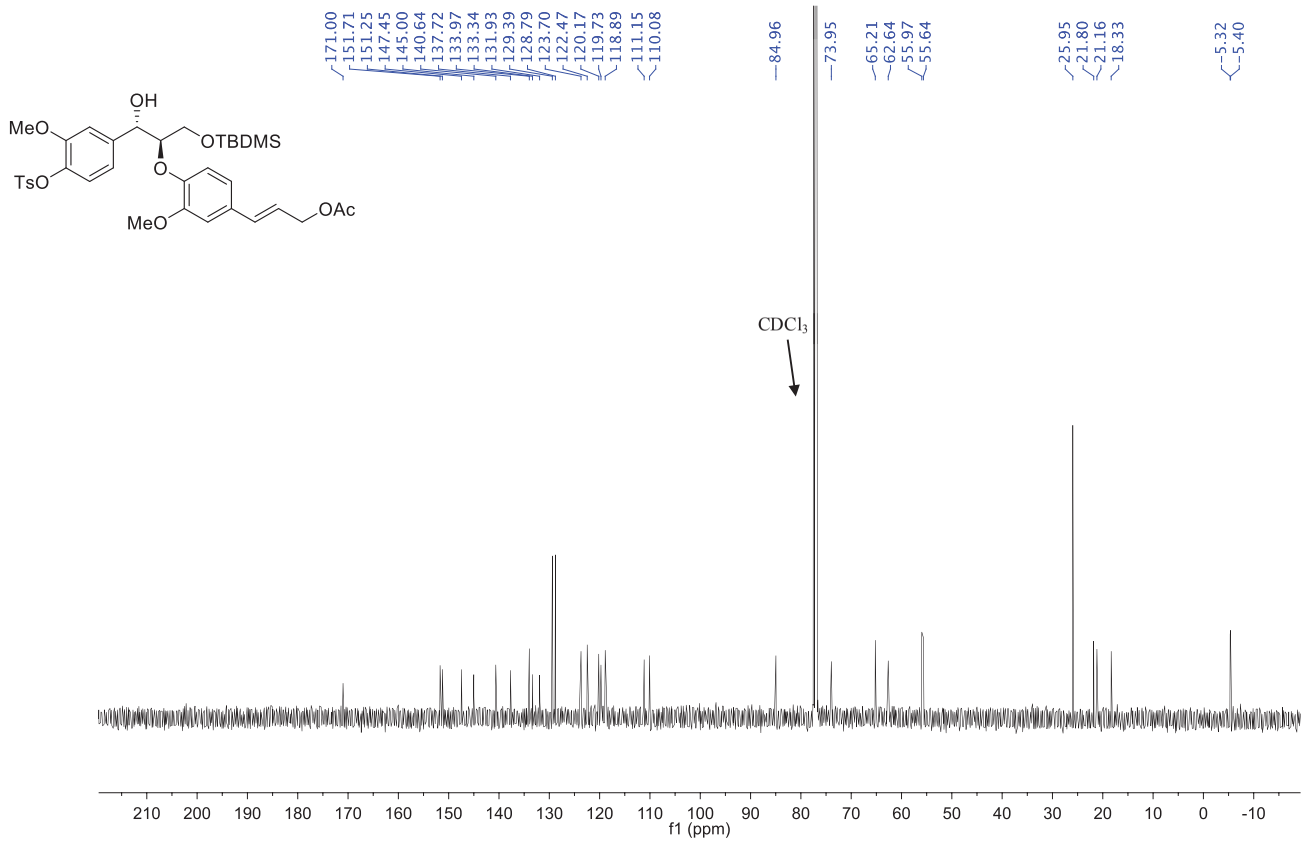


Figure S63. 400 MHz ^{1}H NMR Spectrum of Compound *ent*-**23** (recorded in $CDCl_3$)

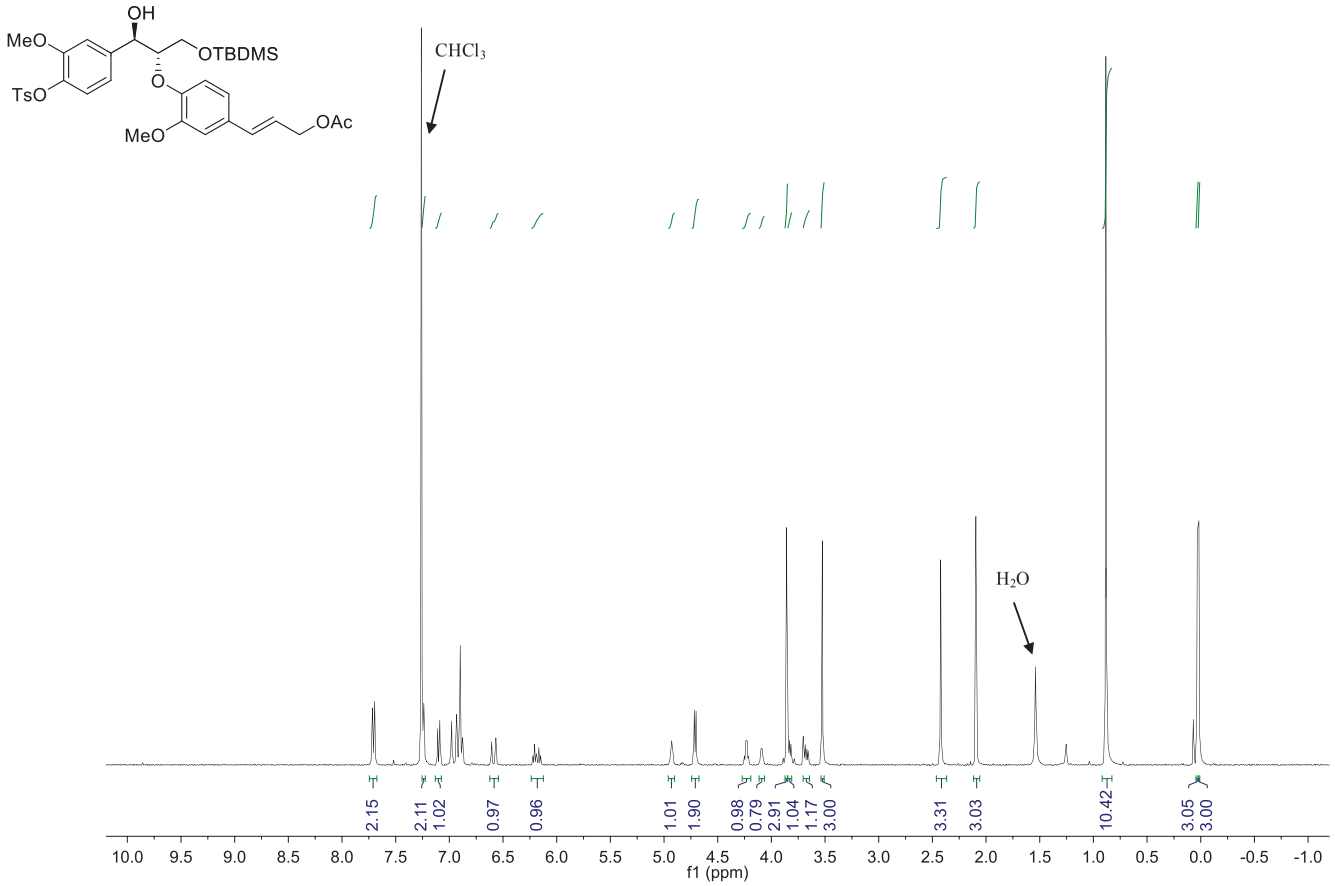
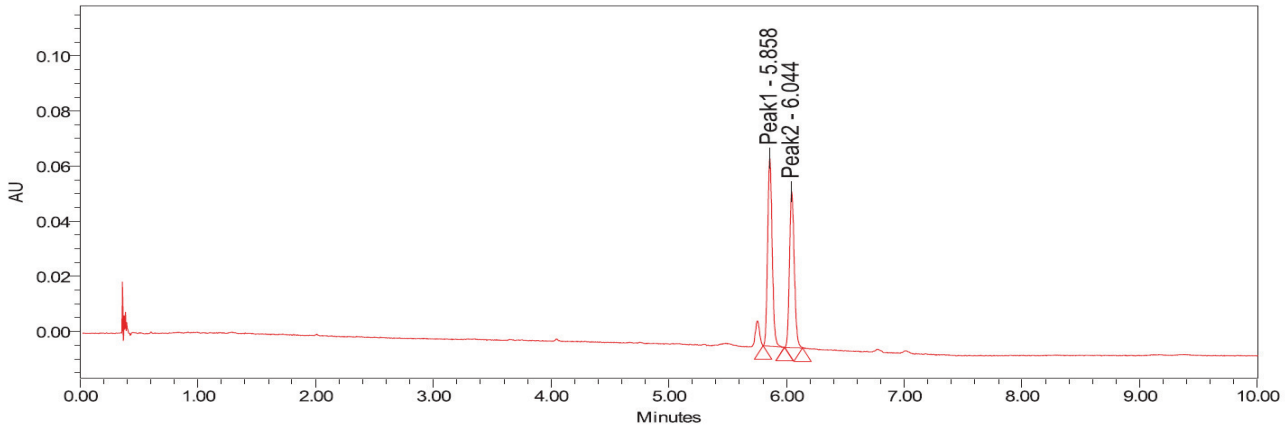
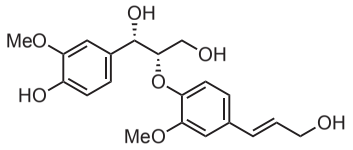


Figure S64. Chiral HPLC Analysis of Compound (±)-1 Conducted on Waters Trefoil CEL1 Column (using 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature = 40 ºC)



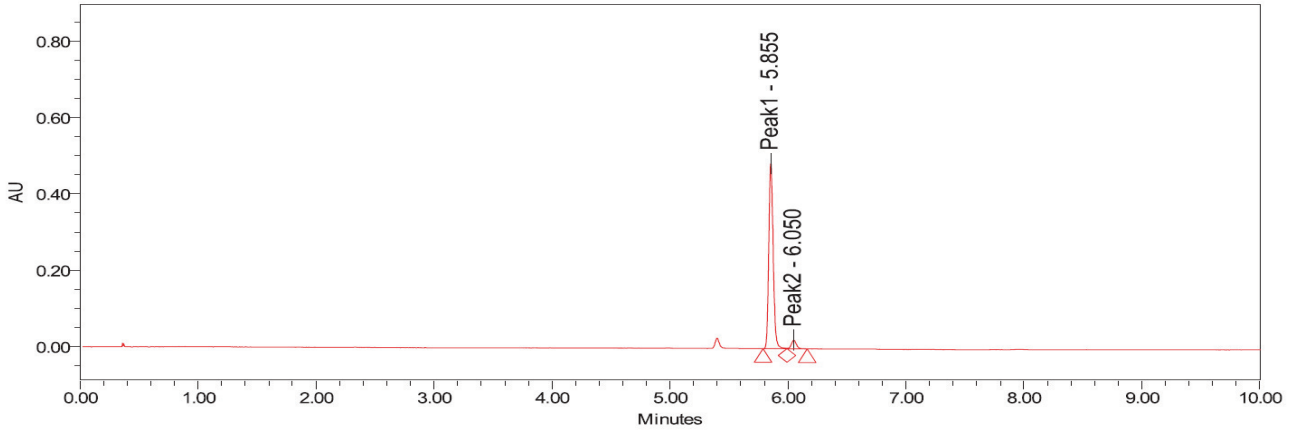
Peak table

Peak #	Retention Time (min)	Area	% Area
Peak 1	5.858	182434	53.21
Peak 2	6.044	160429	46.79
Total		342863	100



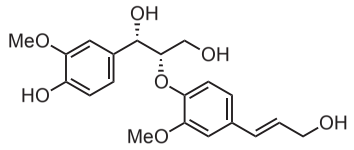
(±)-**1**

Figure S65. Chiral HPLC Analysis of Compound 1 Conducted on Waters Trefoil CEL1 Column (using 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature = 40 ºC)



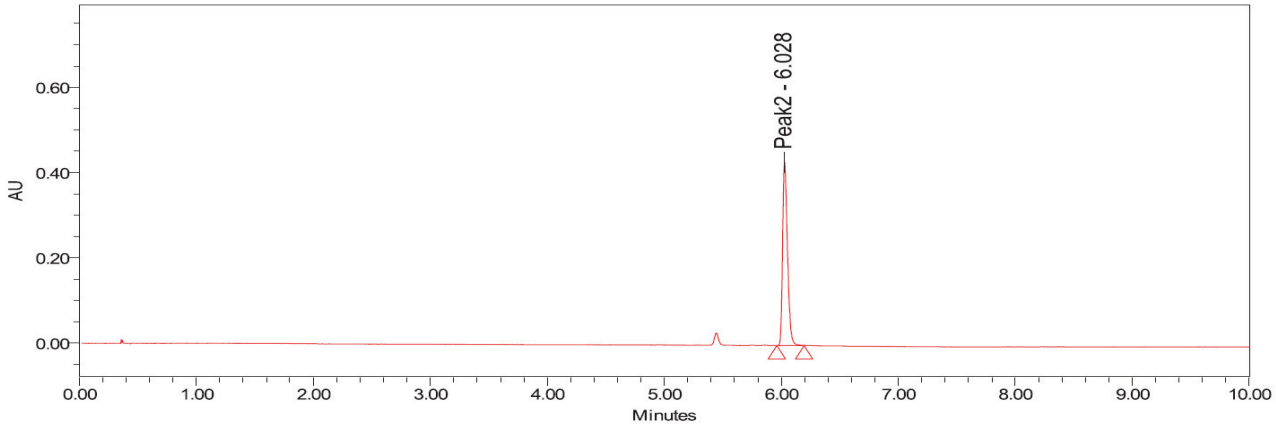
Peak table

Peak #	Retention Time (min)	Area	% Area
Peak 1	5.865	1260000	94.93
Peak 2	6.050	67251	5.07
Total		1327251	100



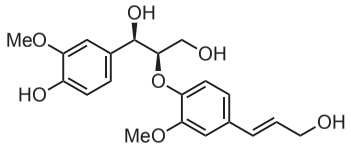
1

Figure S66. Chiral HPLC Analysis of Compound *ent*-1 Conducted on Waters Trefoil CEL1 Column (using 98:2 v/v methanol/supercritical CO_2 elution, flow rate 2 mL/min, temperature = 40 ºC)



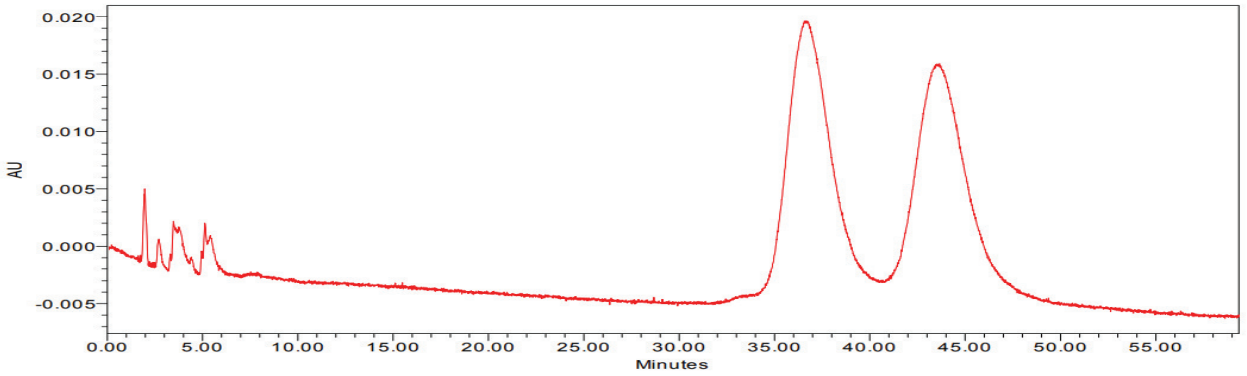
Peak table

Peak #	Retention Time (min)	Area	% Area
Peak 1	5.858	0	0
Peak 2	6.028	1253471	100
Total		1253471	100



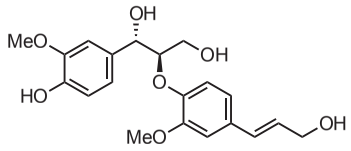
ent-**1**

Figure S67. Chiral HPLC Analysis of Compound (±)-2 Conducted on Chiracel AS-H Column (using 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, temperature = 25 ºC)



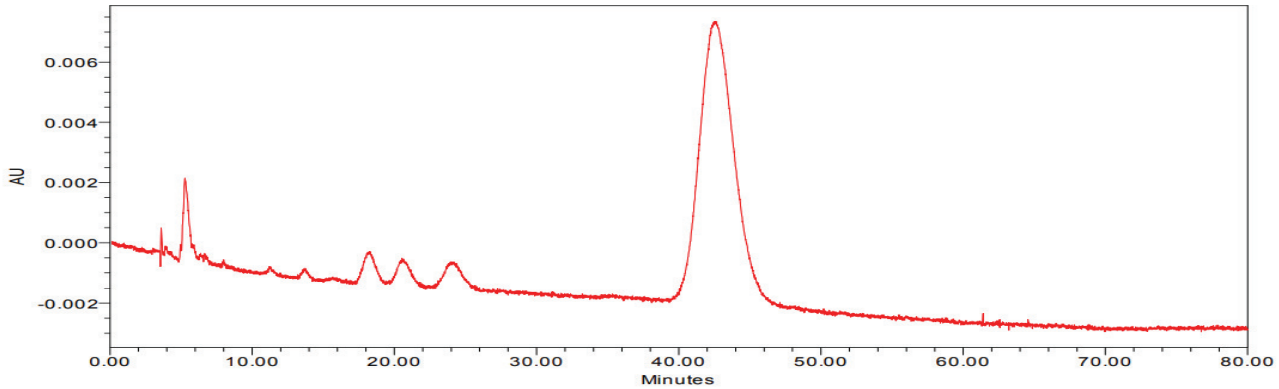
Peak table

Peak #	Retention Time (min)	Area	% Area
Peak 1	36.8	173874	50.95
Peak 2	6.028	167423	49.05
Total		341297	100



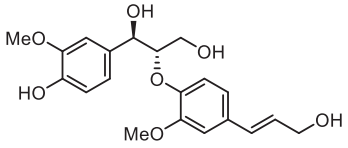
(±)-**2**

Figure S68. Chiral HPLC Analysis of Compound 2 Conducted on Chiracel AS-H Column (using 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, temperature = 25 ºC)



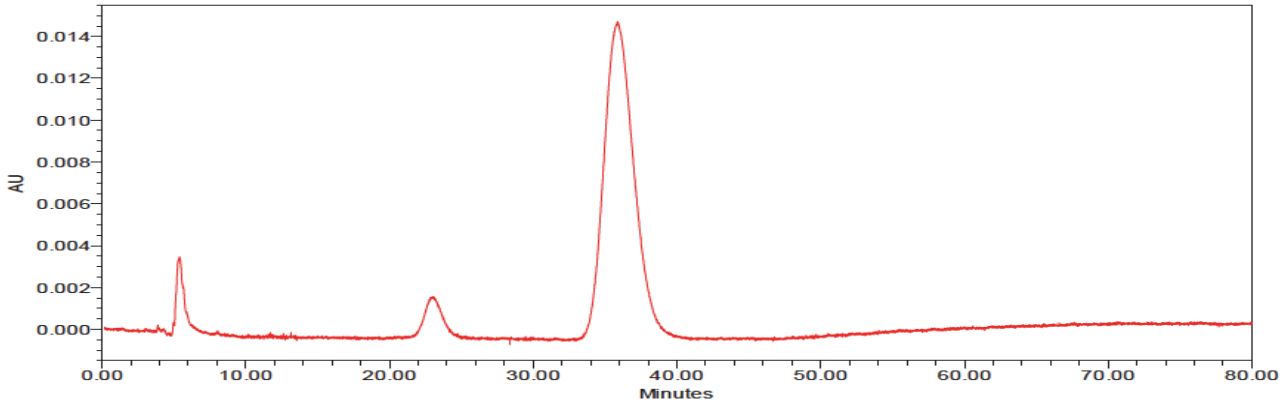
Peak Table

Peak #	Retention Time (min)	Area	% Area
Peak 1	35.8	0	0
Peak 2	43.2	147264	100
Total		147264	100



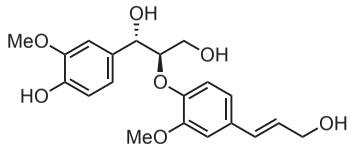
2

Figure S69. Chiral HPLC Analysis of Compound *ent*-2 Conducted on Chiracel AS-H Column (using 85:15 v/v *n*-hexane/ethanol elution, flow rate 1.0 mL/min, temperature = 25 °C)



Peak Table

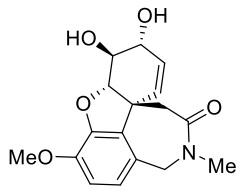
Peak #	Retention Time (min)	Area	% Area
Peak 1	35.8	945726	100
Peak 2	43.2	0	0
Total		945726	100



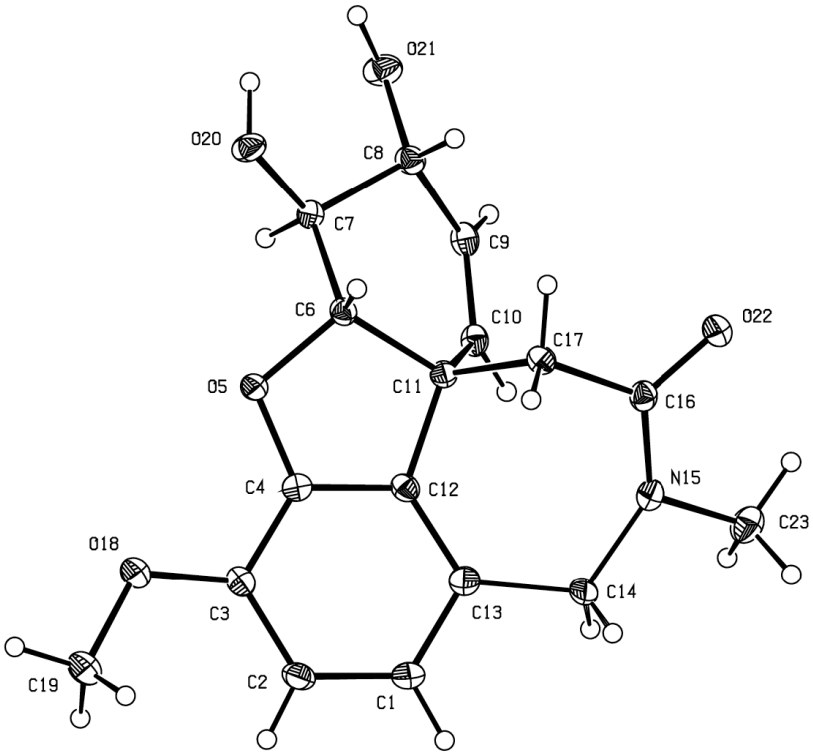
ent-**2**

Appendix One

Single-crystal x-ray report for compound *ent*-**2** of **publication 3**.



ent-**2**



CCDC Deposition Number: **1517512**

Crystal structure of $C_{17}H_{19}NO_5$ — ban16BDS_2

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Abstract

The crystal structure of $C_{17}H_{19}NO_5$ is reported and the absolute structure established.

1. Comment

The crystallographic asymmetric unit consists of one molecule of $C_{17}H_{19}NO_5$. There is disorder in the conformation of the seven-membered ring.

2. Synthesis and crystallization

The compound was prepared by JB and recrystallized from chloroform / methanol. The sample ID is jnb-9–77.

Related literature

Computing details

Data collection: *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014,18:06:01); cell refinement: *CrysAlis PRO* (Agilent Technologies, 2014); data reduction: *CrysAlis PRO* (Agilent Technologies, 2014); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek, 2008); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. 27, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). J. Appl. Cryst. 36, 1487.

CrysAlis PRO, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014,18:06:01)

Flack, H. D. (1983). Acta Cryst. A39, 876-881.

Hooft, R. W. W., Straver, L. H. & Spek, A. L. (2008). J. Appl. Crystallogr., 41, 96-103.

Spek, A. L. (2008). *PLATON*, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

Figure 1

Structure of the $C_{17}H_{19}NO_5$ molecule, with labelling of selected atoms, showing one position only of the disordered atom C14. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2

Structure of the $C_{17}H_{19}NO_5$ molecule, with labelling of selected atoms, showing both positions of the disordered atom (C14 occupancy 0.51; C141 occupancy 0.49). Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

(ban16BDS_2)

Crystal data

$C_{17}H_{19}NO_5$
M_r = 317.34
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
a = 6.58612 (5) Å
b = 9.28140 (8) Å
c = 23.3001 (2) Å
V = 1424.30 (2) Å^3
Z = 4
$F(000)$ = 672
D_x = 1.480 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 13151 reflections
θ = 4–72°
μ = 0.91 mm^{-1}
T = 150 K
Needle, colourless
0.39 × 0.09 × 0.05 mm

Data collection

SuperNova, Dual, Cu at zero, EosS2 diffractometer
Radiation source: Supernova (Cu) X-ray Source
Mirror monochromator
ω scans
Absorption correction: multi-scan *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014,18:06:01) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min} = 0.92, T_{max} = 0.95
19353 measured reflections
2794 independent reflections
2725 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.027
θ_{max} = 72.3°, θ_{min} = 5.1°
h = −5→8
k = −11→11
l = −27→28

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.072
S = 1.01
2794 reflections
225 parameters
10 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H atoms treated by a mixture of independent and constrained refinement
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.28P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: Flack (1983), 1148 Friedel-pairs
Absolute structure parameter: −0.02 (14)

Special details

Refinement. Peaks in a difference electron density map indicated that C14 was disordered over two sites, corresponding to different conformers of the seven-membered ring. The relative occupancies of the two sites were refined. Restraints were imposed on their anisotropic displacement parameters so they would tend to be similar and likewise on the distances to C13 and N15. Inclusion of this disorder lowered the *R*-factor (all data) from 0.040 to 0.028.
Hydrogen atoms attached to C atoms were included at calculated positions, and were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98 Å, O—H 0.87 Å) and with U_{iso}(H) in the range 1.2–1.5 times U_{eq} of the parent atom, after which most were refined with riding constraints, except those bonded to O which were allowed to refine freely and those within the disorder which were included at calculated positions and ride on the atom site to which they are bonded.
The largest peaks in the final difference electron density map are located midway between bonded atoms.
The compound is enantiomerically pure. Its absolute configuration has been determined by refinement of the Flack parameter and is in agreement with the configuration expected on the basis of the synthetic precursors. The final value of the Flack parameter is −0.02 (14) and the final value of the Hooft parameter is −0.04 (6).

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
C1	0.5522 (2)	0.25922 (15)	0.71915 (6)	0.0289	
C2	0.7156 (2)	0.32650 (15)	0.74574 (6)	0.0273	
C3	0.7906 (2)	0.45779 (14)	0.72573 (5)	0.0233	
C4	0.68709 (19)	0.52071 (13)	0.67986 (5)	0.0211	
O5	0.74386 (13)	0.64610 (10)	0.65353 (4)	0.0237	
C6	0.62802 (18)	0.65582 (13)	0.60022 (5)	0.0206	
C7	0.56770 (18)	0.81330 (14)	0.59146 (5)	0.0220	
C8	0.37331 (19)	0.82217 (14)	0.55499 (6)	0.0238	
C9	0.20959 (19)	0.74547 (14)	0.58749 (5)	0.0241	
C10	0.24753 (19)	0.62177 (14)	0.61372 (5)	0.0226	
C11	0.44977 (18)	0.54550 (13)	0.60507 (5)	0.0204	
C12	0.51891 (19)	0.45624 (14)	0.65529 (5)	0.0214	
C13	0.4523 (2)	0.32138 (15)	0.67240 (5)	0.0270	
C14	0.273 (2)	0.2380 (15)	0.6481 (5)	0.0396	0.51 (5)
N15	0.17030 (18)	0.29029 (12)	0.59564 (5)	0.0277	
C16	0.2316 (2)	0.36851 (13)	0.55037 (5)	0.0227	
C17	0.4345 (2)	0.44571 (14)	0.55194 (5)	0.0226	
O18	0.95748 (16)	0.52819 (12)	0.74638 (4)	0.0316	
C19	1.0768 (3)	0.45075 (18)	0.78701 (7)	0.0373	
O20	0.73537 (15)	0.88512 (10)	0.56664 (4)	0.0294	
O21	0.31020 (16)	0.96731 (11)	0.54676 (5)	0.0336	
O22	0.12012 (16)	0.38474 (11)	0.50769 (4)	0.0307	
C23	−0.0320 (2)	0.22463 (16)	0.59403 (7)	0.0334	
C114	0.322 (3)	0.2257 (8)	0.6352 (8)	0.0426	0.49 (5)
H11	0.5149	0.1680	0.7318	0.0357*	
H21	0.7721	0.2824	0.7758	0.0336*	
H61	0.7133	0.6266	0.5687	0.0226*	
H71	0.5387	0.8576	0.6292	0.0239*	
H81	0.4025	0.7770	0.5185	0.0276*	
H91	0.0833	0.7911	0.5889	0.0290*	
H101	0.1445	0.5754	0.6357	0.0288*	
H172	0.4478	0.5049	0.5179	0.0263*	
H171	0.5452	0.3755	0.5518	0.0265*	
H191	1.1974	0.5079	0.7927	0.0556*	
H193	1.1126	0.3601	0.7696	0.0536*	

H192	1.0020	0.4388	0.8221	0.0553*	
H231	−0.0987	0.2445	0.6293	0.0510*	
H233	−0.0260	0.1204	0.5891	0.0493*	
H232	−0.1145	0.2642	0.5628	0.0500*	
H201	0.692 (3)	0.964 (2)	0.5494 (9)	0.0441*	
H211	0.413 (4)	1.009 (3)	0.5202 (10)	0.0512*	
H141	0.1734	0.2343	0.6774	0.0473*	0.51
H142	0.3205	0.1434	0.6401	0.0473*	0.51
H1141	0.2497	0.1638	0.6603	0.0512*	0.49
H1142	0.4123	0.1702	0.6122	0.0512*	0.49

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0333 (7)	0.0272 (6)	0.0261 (6)	−0.0043 (6)	−0.0011 (5)	0.0078 (5)
C2	0.0297 (6)	0.0303 (6)	0.0219 (6)	0.0007 (6)	−0.0026 (5)	0.0066 (5)
C3	0.0218 (6)	0.0274 (6)	0.0208 (6)	0.0005 (5)	−0.0017 (5)	0.0000 (5)
C4	0.0213 (6)	0.0205 (6)	0.0215 (6)	0.0016 (5)	0.0025 (4)	0.0006 (5)
O5	0.0217 (4)	0.0234 (4)	0.0261 (4)	−0.0024 (3)	−0.0067 (3)	0.0058 (3)
C6	0.0182 (5)	0.0240 (6)	0.0197 (6)	−0.0012 (5)	−0.0011 (4)	0.0013 (4)
C7	0.0199 (5)	0.0230 (5)	0.0232 (5)	−0.0025 (5)	−0.0016 (5)	0.0017 (5)
C8	0.0208 (6)	0.0251 (6)	0.0254 (6)	0.0021 (5)	−0.0021 (5)	0.0029 (5)
C9	0.0176 (5)	0.0292 (6)	0.0256 (6)	0.0010 (5)	−0.0001 (5)	−0.0042 (5)
C10	0.0188 (6)	0.0273 (6)	0.0219 (6)	−0.0021 (5)	0.0014 (4)	−0.0027 (5)
C11	0.0202 (5)	0.0223 (5)	0.0188 (5)	−0.0020 (5)	0.0003 (4)	0.0011 (5)
C12	0.0220 (6)	0.0251 (6)	0.0172 (5)	0.0006 (5)	0.0004 (4)	0.0003 (5)
C13	0.0300 (6)	0.0281 (6)	0.0230 (6)	−0.0046 (6)	0.0000 (5)	0.0026 (5)
C14	0.053 (4)	0.047 (3)	0.019 (3)	−0.029 (3)	−0.012 (2)	0.015 (2)
N15	0.0295 (6)	0.0261 (5)	0.0275 (5)	−0.0076 (5)	−0.0031 (5)	0.0008 (4)
C16	0.0236 (6)	0.0208 (5)	0.0236 (6)	0.0008 (5)	−0.0014 (5)	−0.0034 (5)
C17	0.0236 (6)	0.0245 (6)	0.0195 (5)	0.0005 (5)	−0.0001 (5)	−0.0001 (5)
O18	0.0290 (5)	0.0328 (5)	0.0329 (5)	−0.0029 (4)	−0.0115 (4)	0.0070 (4)
C19	0.0337 (7)	0.0399 (8)	0.0383 (8)	−0.0002 (6)	−0.0147 (6)	0.0082 (7)
O20	0.0203 (5)	0.0270 (5)	0.0409 (5)	−0.0023 (4)	−0.0018 (4)	0.0118 (4)
O21	0.0246 (5)	0.0296 (5)	0.0467 (6)	0.0047 (4)	0.0000 (4)	0.0111 (4)
O22	0.0292 (5)	0.0334 (5)	0.0293 (5)	−0.0046 (4)	−0.0084 (4)	0.0043 (4)
C23	0.0295 (7)	0.0332 (7)	0.0375 (7)	−0.0077 (6)	0.0051 (6)	−0.0003 (6)
C114	0.065 (4)	0.030 (2)	0.033 (4)	−0.020 (2)	−0.013 (4)	0.013 (2)

Geometric parameters (Å, º)

C1—C2	1.390 (2)	C12—C13	1.3849 (19)
C1—C13	1.397 (2)	C13—C14	1.519 (6)
C1—H11	0.929	C13—C114	1.508 (7)
C2—C3	1.3952 (19)	C14—N15	1.480 (6)
C2—H21	0.892	C14—H141	0.950
C3—C4	1.3957 (17)	C14—H142	0.950
C3—O18	1.3661 (17)	N15—C16	1.3427 (18)
C4—O5	1.3678 (15)	N15—C23	1.4656 (17)
C4—C12	1.3830 (18)	N15—C114	1.486 (7)
O5—C6	1.4604 (14)	C16—C17	1.5169 (18)
C6—C7	1.5283 (17)	C16—O22	1.2452 (17)

C6—C11	1.5619 (16)	C17—H172	0.969
C6—H61	0.963	C17—H171	0.978
C7—C8	1.5389 (16)	O18—C19	1.4249 (17)
C7—O20	1.4136 (15)	C19—H191	0.964
C7—H71	0.989	C19—H193	0.963
C8—C9	1.4976 (18)	C19—H192	0.962
C8—O21	1.4227 (16)	O20—H201	0.88 (2)
C8—H81	0.967	O21—H211	1.00 (2)
C9—C10	1.3245 (19)	C23—H231	0.951
C9—H91	0.934	C23—H233	0.975
C10—C11	1.5218 (17)	C23—H232	0.979
C10—H101	0.952	C114—H1141	0.950
C11—C12	1.5044 (16)	C114—H1142	0.950
C11—C17	1.5493 (17)		
O5···O18	2.8031 (13)	O20···O22^{iii}	2.8528 (14)
O5···O20	3.0039 (13)	O21···O22^{iii}	2.7680 (15)
O5···C19^{i}	3.3630 (19)	N15···C10	3.1467 (17)
O20···C9^{ii}	3.4163 (16)	C1···C4^{iv}	3.5946 (18)
O20···O21	2.9390 (14)	C8···C17	3.5180 (18)
C2—C1—C13	121.77 (13)	C1—C13—C12	116.64 (12)
C2—C1—H11	118.2	C1—C13—C14	116.5 (3)
C13—C1—H11	119.9	C12—C13—C14	126.8 (3)
C1—C2—C3	121.18 (12)	C1—C13—C114	118.2 (4)
C1—C2—H21	117.8	C12—C13—C114	123.1 (5)
C3—C2—H21	121.0	C13—C14—N15	119.8 (5)
C2—C3—C4	116.63 (12)	C13—C14—H141	106.8
C2—C3—O18	125.81 (12)	N15—C14—H141	106.8
C4—C3—O18	117.55 (11)	C13—C14—H142	106.9
C3—C4—O5	124.47 (11)	N15—C14—H142	106.9
C3—C4—C12	121.81 (12)	H141—C14—H142	109.5
O5—C4—C12	113.67 (11)	C14—N15—C16	133.5 (5)
C4—O5—C6	106.93 (9)	C14—N15—C23	107.6 (4)
O5—C6—C7	107.96 (9)	C16—N15—C23	118.55 (12)
O5—C6—C11	106.90 (9)	C16—N15—C114	120.1 (9)
C7—C6—C11	116.18 (10)	C23—N15—C114	117.4 (7)
O5—C6—H61	109.0	N15—C16—C17	120.08 (11)
C7—C6—H61	108.6	N15—C16—O22	121.05 (12)
C11—C6—H61	108.0	C17—C16—O22	118.79 (11)
C6—C7—C8	109.95 (10)	C11—C17—C16	111.03 (10)
C6—C7—O20	107.61 (10)	C11—C17—H172	108.0
C8—C7—O20	113.50 (10)	C16—C17—H172	109.1
C6—C7—H71	109.2	C11—C17—H171	110.6
C8—C7—H71	107.9	C16—C17—H171	110.0
O20—C7—H71	108.6	H172—C17—H171	108.0
C7—C8—C9	107.12 (10)	C3—O18—C19	115.88 (11)
C7—C8—O21	111.60 (11)	O18—C19—H191	105.6
C9—C8—O21	107.93 (11)	O18—C19—H193	107.2
C7—C8—H81	107.3	H191—C19—H193	109.7
C9—C8—H81	112.4	O18—C19—H192	109.9
O21—C8—H81	110.5	H191—C19—H192	111.6

C8—C9—C10	120.64 (11)	H193—C19—H192	112.5
C8—C9—H91	116.4	C7—O20—H201	109.0 (14)
C10—C9—H91	123.0	C8—O21—H211	104.4 (13)
C9—C10—C11	120.48 (11)	N15—C23—H231	108.5
C9—C10—H101	120.3	N15—C23—H233	112.3
C11—C10—H101	119.0	H231—C23—H233	108.2
C10—C11—C6	111.26 (10)	N15—C23—H232	111.6
C10—C11—C12	114.71 (10)	H231—C23—H232	108.3
C6—C11—C12	100.94 (10)	H233—C23—H232	107.9
C10—C11—C17	109.09 (10)	C13—C114—N15	120.1 (5)
C6—C11—C17	112.52 (10)	C13—C114—H1141	106.7
C12—C11—C17	108.18 (10)	N15—C114—H1141	106.7
C11—C12—C4	109.03 (11)	C13—C114—H1142	106.8
C11—C12—C13	128.73 (12)	N15—C114—H1142	106.8
C4—C12—C13	121.71 (12)	H1141—C114—H1142	109.5

C4—O5—C6—C11	15.88 (12)	O5—C6—C11—C17	−129.75 (10)
C6—O5—C4—C3	166.66 (11)	O5—C6—C11—C10	107.49 (10)
C4—O5—C6—C7	141.56 (10)	C7—C6—C11—C12	−135.23 (10)
C6—O5—C4—C12	−10.82 (13)	C7—C6—C11—C10	−13.08 (14)
C19—O18—C3—C4	−170.74 (12)	C6—C7—C8—O21	178.94 (10)
C19—O18—C3—C2	8.03 (19)	O20—C7—C8—C9	−178.41 (10)
C16—N15—C14—C13	27.6 (13)	O20—C7—C8—O21	−60.47 (14)
C14—N15—C16—O22	171.6 (7)	C6—C7—C8—C9	61.01 (13)
C14—N15—C16—C17	−11.9 (7)	C7—C8—C9—C10	−42.31 (16)
C23—N15—C14—C13	−159.9 (7)	O21—C8—C9—C10	−162.61 (12)
C23—N15—C16—C17	176.24 (11)	C8—C9—C10—C11	−7.89 (18)
C23—N15—C16—O22	−0.35 (18)	C9—C10—C11—C17	−87.98 (14)
C2—C1—C13—C12	−2.5 (2)	C9—C10—C11—C6	36.72 (15)
C13—C1—C2—C3	−1.8 (2)	C9—C10—C11—C12	150.50 (12)
C2—C1—C13—C14	−178.7 (6)	C6—C11—C17—C16	−164.98 (10)
C1—C2—C3—O18	−175.65 (12)	C10—C11—C17—C16	−41.01 (13)
C1—C2—C3—C4	3.13 (19)	C12—C11—C17—C16	84.39 (12)
O18—C3—C4—O5	1.44 (18)	C6—C11—C12—C13	−163.07 (13)
C2—C3—C4—O5	−177.45 (12)	C10—C11—C12—C4	−111.06 (12)
O18—C3—C4—C12	178.72 (11)	C10—C11—C12—C13	77.23 (16)
C2—C3—C4—C12	−0.16 (18)	C17—C11—C12—C4	126.93 (11)
O5—C4—C12—C13	173.24 (11)	C17—C11—C12—C13	−44.78 (17)
C3—C4—C12—C11	−176.72 (11)	C6—C11—C12—C4	8.64 (13)
C3—C4—C12—C13	−4.32 (19)	C4—C12—C13—C14	−178.7 (6)
O5—C4—C12—C11	0.83 (14)	C4—C12—C13—C1	5.53 (19)
C11—C6—C7—C8	−33.81 (14)	C11—C12—C13—C1	176.31 (12)
O5—C6—C7—O20	82.12 (11)	C11—C12—C13—C14	−7.9 (6)
O5—C6—C7—C8	−153.80 (10)	C12—C13—C14—N15	9.4 (12)
C11—C6—C7—O20	−157.89 (10)	C1—C13—C14—N15	−174.8 (6)
C7—C6—C11—C17	109.68 (12)	O22—C16—C17—C11	121.81 (12)
O5—C6—C11—C12	−14.66 (11)	N15—C16—C17—C11	−54.85 (15)

Symmetry codes: (i) −*x*+2, *y*+1/2, −*z*+3/2; (ii) *x*+1, *y*, *z*; (iii) *x*+1/2, −*y*+3/2, −*z*+1; (iv) −*x*+1, *y*−1/2, −*z*+3/2.

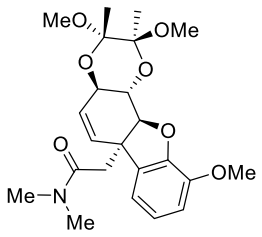
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O20—H201···O22^{iii}	0.88 (2)	1.99 (2)	2.8528 (14)	165.1 (19)
O21—H211···O22^{iii}	1.00 (2)	1.80 (2)	2.7680 (15)	162 (2)

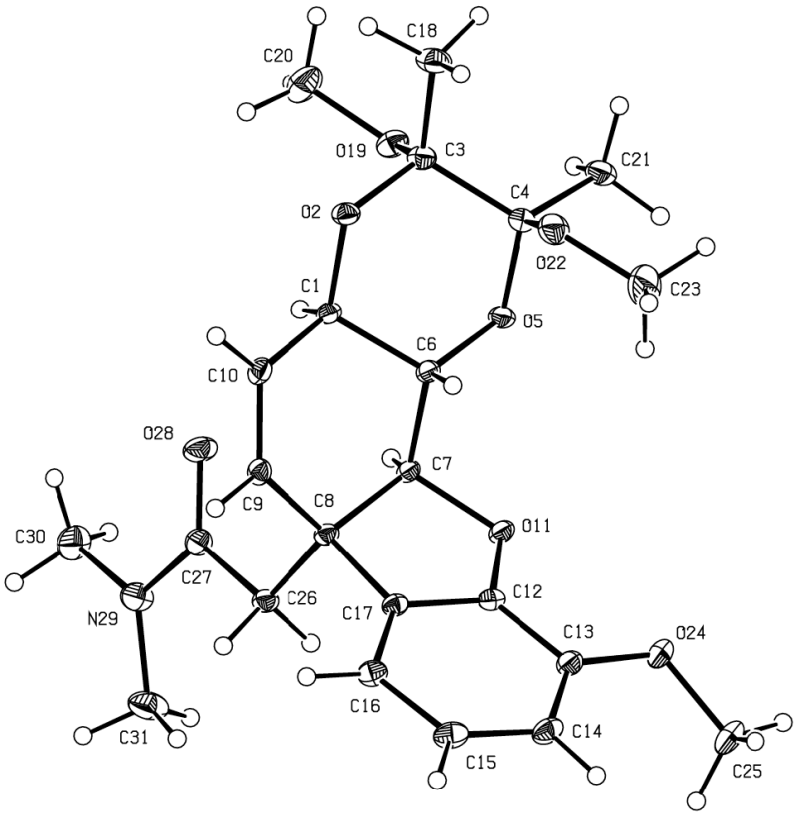
Symmetry code: (iii) $x+1/2, -y+3/2, -z+1$.

Appendix Two

Single-crystal x-ray report for compound *ent*-**15** of **publication 3**.



ent-**15**



CCDC Deposition Number: **1517513**

Crystal structure of $C_{23}H_{31}NO_7$ — ban1509SN_Brett

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Abstract

The crystal structure of $C_{23}H_{31}NO_7$ is reported and the absolute structure established.

1. Comment

The crystallographic asymmetric unit consists of one molecule of $C_{23}H_{31}NO_7$.

2. Synthesis and crystallization

The compound was prepared by JB and recrystallized from dichloromethane/diethyl ether/ methanol. The sample ID is jmb-9–51 A.

Related literature

Computing details

Data collection: *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014,18:06:01); cell refinement: *CrysAlis PRO* (Agilent Technologies, 2014); data reduction: *CrysAlis PRO* (Agilent Technologies, 2014); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek, 2008); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

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Figure 1

Structure of the $C_{23}H_{31}NO_7$ molecule with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

(ban1509SN_Brett)

Crystal data

$C_{23}H_{31}NO_7$
M_r = 433.50
Monoclinic, $P2_1$
Hall symbol: p 2yb
a = 10.14845 (9) Å
b = 10.61199 (7) Å
c = 10.80864 (10) Å
β = 106.8796 (9)°
V = 1113.89 (2) Å^3
Z = 2
$F(000)$ = 464
D_x = 1.292 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 12487 reflections
θ = 4–72°
μ = 0.79 mm^{-1}
T = 150 K
Needle, colourless
0.34 × 0.08 × 0.04 mm

Data collection

SuperNova, Dual, Cu at zero, EosS2 diffractometer
Radiation source: Supernova (Cu) X-ray Source
Mirror monochromator
ω scans
Absorption correction: multi-scan *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014,18:06:01) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min} = 0.72, T_{max} = 0.97
17464 measured reflections
3907 independent reflections
3843 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.032
θ_{max} = 72.4°, θ_{min} = 4.3°
h = −12→12
k = −12→13
l = −13→13

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.067
S = 1.03
3907 reflections
282 parameters
1 restraint
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.14P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.0004
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.13 e Å^{-3}
Extinction correction: Larson (1970), Equation 22
Extinction coefficient: 21 (3)
Absolute structure: Flack (1983), 1570 Friedel-pairs
Absolute structure parameter: 0.09 (10)

Special details

Refinement. The compound is enantiomerically pure. Its absolute configuration has been determined by refinement of the Flack parameter and is in agreement with the configuration expected on the basis of the synthetic precursors. The final value of the Flack parameter is 0.09 (10) and the final value of the Hooft parameter is 0.00 (7).
Hydrogen atoms attached to C atoms were included at calculated positions, and were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2–1.5 times U_{eq} of the parent atom, after which they were refined with riding constraints
The largest peaks in the final difference electron density map are located midway between bonded atoms.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.68397 (11)	0.12146 (13)	0.24852 (11)	0.0178

O2	0.69191 (9)	0.05159 (10)	0.13747 (8)	0.0207
C3	0.66963 (12)	0.12657 (14)	0.02327 (12)	0.0215
C4	0.53152 (12)	0.20050 (14)	−0.00328 (12)	0.0231
O5	0.53002 (8)	0.27131 (10)	0.10856 (8)	0.0215
C6	0.54858 (11)	0.19312 (12)	0.21922 (11)	0.0172
C7	0.55139 (10)	0.27620 (13)	0.33351 (10)	0.0164
C8	0.57458 (11)	0.19710 (12)	0.45943 (11)	0.0166
C9	0.64030 (12)	0.07002 (13)	0.45414 (12)	0.0192
C10	0.68960 (12)	0.03377 (13)	0.35872 (12)	0.0203
O11	0.41817 (8)	0.33869 (10)	0.31116 (8)	0.0192
C12	0.34747 (11)	0.27105 (13)	0.37928 (10)	0.0180
C13	0.20875 (11)	0.29248 (13)	0.36978 (11)	0.0215
C14	0.15121 (12)	0.21836 (15)	0.44776 (13)	0.0254
C15	0.23064 (13)	0.12909 (15)	0.53224 (13)	0.0269
C16	0.36976 (12)	0.11191 (14)	0.54307 (12)	0.0219
C17	0.42633 (11)	0.18470 (13)	0.46415 (11)	0.0174
C18	0.67134 (15)	0.03480 (14)	−0.08280 (13)	0.0298
O19	0.77102 (9)	0.22285 (11)	0.04139 (9)	0.0255
C20	0.90866 (14)	0.18089 (18)	0.06163 (18)	0.0406
C21	0.50951 (15)	0.29615 (16)	−0.11129 (12)	0.0316
O22	0.42984 (9)	0.10483 (12)	−0.02852 (9)	0.0309
C23	0.29151 (15)	0.1473 (2)	−0.05368 (18)	0.0503
O24	0.14336 (9)	0.38443 (11)	0.28649 (9)	0.0286
C25	0.01963 (15)	0.43452 (18)	0.30613 (16)	0.0401
C26	0.65308 (11)	0.27385 (13)	0.57976 (11)	0.0198
C27	0.80111 (11)	0.30543 (13)	0.58562 (12)	0.0218
O28	0.84873 (8)	0.27846 (12)	0.49696 (9)	0.0305
N29	0.87777 (11)	0.36387 (13)	0.69404 (11)	0.0286
C30	1.01889 (13)	0.39769 (17)	0.70098 (15)	0.0355
C31	0.81968 (15)	0.42350 (18)	0.78773 (14)	0.0373
H11	0.7589	0.1833	0.2735	0.0199*
H61	0.4722	0.1310	0.2071	0.0211*
H71	0.6196	0.3421	0.3400	0.0194*
H91	0.6437	0.0138	0.5232	0.0244*
H101	0.7282	−0.0477	0.3601	0.0256*
H141	0.0599	0.2282	0.4467	0.0307*
H151	0.1911	0.0796	0.5833	0.0318*
H161	0.4234	0.0520	0.6007	0.0256*
H181	0.6663	0.0801	−0.1615	0.0453*
H183	0.7555	−0.0161	−0.0597	0.0456*
H182	0.5944	−0.0223	−0.0970	0.0441*
H201	0.9681	0.2576	0.0764	0.0599*
H203	0.9173	0.1406	−0.0152	0.0608*
H202	0.9376	0.1253	0.1354	0.0623*
H211	0.4235	0.3395	−0.1212	0.0463*
H212	0.5832	0.3568	−0.0908	0.0457*
H213	0.5075	0.2528	−0.1921	0.0465*
H232	0.2350	0.0755	−0.0457	0.0741*
H231	0.2559	0.1834	−0.1416	0.0733*
H233	0.2818	0.2118	0.0082	0.0743*
H252	−0.0042	0.5053	0.2483	0.0588*
H251	0.0338	0.4603	0.3957	0.0584*

H253	−0.0519	0.3724	0.2831	0.0586*
H261	0.6050	0.3530	0.5826	0.0249*
H262	0.6531	0.2268	0.6558	0.0243*
H301	1.0739	0.4002	0.7910	0.0535*
H302	1.0240	0.4794	0.6648	0.0532*
H303	1.0563	0.3344	0.6549	0.0531*
H311	0.8861	0.4222	0.8729	0.0569*
H312	0.8035	0.5125	0.7670	0.0585*
H313	0.7359	0.3828	0.7908	0.0575*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0181 (5)	0.0183 (6)	0.0189 (5)	0.0029 (4)	0.0082 (4)	−0.0006 (5)
O2	0.0264 (4)	0.0183 (5)	0.0201 (4)	0.0039 (3)	0.0109 (3)	−0.0004 (3)
C3	0.0259 (6)	0.0203 (6)	0.0209 (5)	0.0008 (5)	0.0111 (4)	0.0005 (5)
C4	0.0247 (6)	0.0276 (7)	0.0183 (5)	0.0031 (5)	0.0081 (4)	−0.0007 (5)
O5	0.0279 (4)	0.0221 (5)	0.0170 (4)	0.0066 (4)	0.0106 (3)	0.0031 (4)
C6	0.0179 (5)	0.0173 (6)	0.0182 (5)	0.0027 (4)	0.0079 (4)	0.0018 (4)
C7	0.0148 (5)	0.0172 (5)	0.0189 (5)	0.0020 (4)	0.0073 (4)	0.0008 (5)
C8	0.0157 (5)	0.0181 (6)	0.0180 (5)	0.0000 (4)	0.0079 (4)	0.0007 (4)
C9	0.0189 (5)	0.0181 (6)	0.0209 (5)	0.0021 (4)	0.0062 (4)	0.0047 (4)
C10	0.0185 (5)	0.0188 (6)	0.0239 (6)	0.0042 (4)	0.0063 (4)	0.0026 (5)
O11	0.0180 (4)	0.0204 (4)	0.0224 (4)	0.0044 (3)	0.0107 (3)	0.0036 (3)
C12	0.0184 (5)	0.0188 (6)	0.0185 (5)	−0.0011 (4)	0.0081 (4)	−0.0033 (5)
C13	0.0171 (5)	0.0252 (7)	0.0222 (5)	0.0008 (5)	0.0060 (4)	−0.0041 (5)
C14	0.0168 (5)	0.0303 (7)	0.0318 (6)	−0.0025 (5)	0.0113 (5)	−0.0046 (6)
C15	0.0253 (6)	0.0290 (7)	0.0320 (6)	−0.0067 (5)	0.0173 (5)	−0.0009 (6)
C16	0.0224 (6)	0.0207 (6)	0.0251 (6)	−0.0025 (5)	0.0109 (4)	0.0008 (5)
C17	0.0156 (5)	0.0187 (6)	0.0194 (5)	−0.0019 (4)	0.0074 (4)	−0.0023 (4)
C18	0.0430 (7)	0.0263 (7)	0.0245 (6)	0.0037 (6)	0.0165 (5)	−0.0032 (6)
O19	0.0256 (4)	0.0233 (5)	0.0314 (4)	−0.0003 (4)	0.0143 (4)	0.0003 (4)
C20	0.0263 (7)	0.0437 (9)	0.0558 (10)	0.0014 (6)	0.0183 (6)	0.0042 (8)
C21	0.0420 (7)	0.0358 (8)	0.0204 (6)	0.0134 (6)	0.0147 (5)	0.0057 (6)
O22	0.0256 (4)	0.0397 (6)	0.0256 (4)	−0.0042 (4)	0.0048 (3)	−0.0049 (4)
C23	0.0241 (7)	0.0777 (15)	0.0436 (9)	−0.0035 (8)	0.0011 (6)	0.0016 (9)
O24	0.0197 (4)	0.0364 (6)	0.0304 (5)	0.0098 (4)	0.0087 (3)	0.0037 (4)
C25	0.0245 (6)	0.0524 (10)	0.0449 (8)	0.0179 (7)	0.0127 (6)	0.0053 (8)
C26	0.0178 (5)	0.0246 (6)	0.0185 (5)	−0.0014 (5)	0.0077 (4)	−0.0015 (5)
C27	0.0179 (5)	0.0255 (7)	0.0223 (5)	−0.0028 (4)	0.0064 (4)	−0.0007 (5)
O28	0.0188 (4)	0.0464 (6)	0.0296 (5)	−0.0059 (4)	0.0121 (3)	−0.0105 (4)
N29	0.0217 (5)	0.0391 (7)	0.0256 (5)	−0.0097 (5)	0.0079 (4)	−0.0065 (5)
C30	0.0200 (6)	0.0464 (9)	0.0385 (7)	−0.0088 (6)	0.0058 (5)	−0.0092 (7)
C31	0.0344 (7)	0.0526 (10)	0.0278 (6)	−0.0155 (7)	0.0137 (5)	−0.0140 (7)

Geometric parameters (Å, º)

C1—O2	1.4329 (14)	C16—H161	0.944
C1—C6	1.5211 (14)	C18—H181	0.966
C1—C10	1.4995 (17)	C18—H183	0.980
C1—H11	0.981	C18—H182	0.965
O2—C3	1.4303 (15)	O19—C20	1.4213 (16)

C3—C4	1.5584 (16)	C20—H201	0.998
C3—C18	1.5082 (17)	C20—H203	0.961
C3—O19	1.4227 (16)	C20—H202	0.966
C4—O5	1.4272 (14)	C21—H211	0.965
C4—C21	1.5138 (18)	C21—H212	0.962
C4—O22	1.4165 (17)	C21—H213	0.982
O5—C6	1.4226 (14)	O22—C23	1.4234 (18)
C6—C7	1.5112 (15)	C23—H232	0.973
C6—H61	0.996	C23—H231	0.991
C7—C8	1.5577 (15)	C23—H233	0.982
C7—O11	1.4616 (12)	O24—C25	1.4349 (15)
C7—H71	0.972	C25—H252	0.962
C8—C9	1.5128 (17)	C25—H251	0.976
C8—C17	1.5258 (14)	C25—H253	0.958
C8—C26	1.5453 (16)	C26—C27	1.5224 (14)
C9—C10	1.3274 (17)	C26—H261	0.976
C9—H91	0.949	C26—H262	0.961
C10—H101	0.948	C27—O28	1.2259 (15)
O11—C12	1.3707 (14)	C27—N29	1.3541 (16)
C12—C13	1.4001 (14)	N29—C30	1.4570 (15)
C12—C17	1.3767 (17)	N29—C31	1.4561 (18)
C13—C14	1.3985 (18)	C30—H301	0.972
C13—O24	1.3624 (16)	C30—H302	0.959
C14—C15	1.398 (2)	C30—H303	0.976
C14—H141	0.929	C31—H311	0.971
C15—C16	1.3944 (17)	C31—H312	0.974
C15—H151	0.932	C31—H313	0.963
C16—C17	1.3923 (17)		

O2···O5	2.8170 (14)	O28···C10	3.1909 (18)
O2···O22	2.8001 (13)	O28···C14^{iv}	3.3257 (16)
O2···C21^{i}	3.3572 (19)	O28···C7	3.0218 (14)
O2···C30^{ii}	3.3696 (18)	O28···C9	3.0021 (17)
O5···O19	2.7937 (13)	O28···C1	3.1898 (16)
O5···O11	2.8352 (12)	C1···C20	3.515 (2)
O11···O24	2.7664 (13)	C6···C23	3.358 (2)
O11···C18^{iii}	3.1538 (17)	C9···C13^{v}	3.5987 (19)
O19···C6	3.3778 (15)	C10···C30^{ii}	3.516 (2)
O22···C1	3.3413 (15)		

O2—C1—C6	110.57 (9)	C8—C17—C16	130.87 (11)
O2—C1—C10	110.23 (10)	C8—C17—C12	107.96 (10)
C6—C1—C10	107.43 (9)	C16—C17—C12	120.94 (10)
O2—C1—H11	110.4	C3—C18—H181	109.8
C6—C1—H11	107.7	C3—C18—H183	111.3
C10—C1—H11	110.4	H181—C18—H183	108.5
C1—O2—C3	113.69 (9)	C3—C18—H182	109.8
O2—C3—C4	110.33 (9)	H181—C18—H182	109.8
O2—C3—C18	105.25 (11)	H183—C18—H182	107.4
C4—C3—C18	113.16 (10)	C3—O19—C20	115.81 (11)
O2—C3—O19	110.73 (9)	O19—C20—H201	106.9
C4—C3—O19	103.86 (10)	O19—C20—H203	109.8

C18—C3—O19	113.63 (10)	H201—C20—H203	107.4
C3—C4—O5	109.83 (9)	O19—C20—H202	111.6
C3—C4—C21	113.77 (10)	H201—C20—H202	110.0
O5—C4—C21	105.35 (11)	H203—C20—H202	111.0
C3—C4—O22	103.92 (10)	C4—C21—H211	109.4
O5—C4—O22	110.74 (9)	C4—C21—H212	109.9
C21—C4—O22	113.33 (11)	H211—C21—H212	108.9
C4—O5—C6	111.94 (9)	C4—C21—H213	109.4
C1—C6—O5	110.96 (9)	H211—C21—H213	109.9
C1—C6—C7	108.66 (9)	H212—C21—H213	109.4
O5—C6—C7	108.27 (10)	C4—O22—C23	115.64 (13)
C1—C6—H61	108.5	O22—C23—H232	108.0
O5—C6—H61	111.5	O22—C23—H231	111.7
C7—C6—H61	108.8	H232—C23—H231	109.1
C6—C7—C8	111.22 (10)	O22—C23—H233	112.3
C6—C7—O11	109.43 (8)	H232—C23—H233	107.9
C8—C7—O11	106.67 (8)	H231—C23—H233	107.7
C6—C7—H71	108.8	C13—O24—C25	116.54 (11)
C8—C7—H71	113.7	O24—C25—H252	105.0
O11—C7—H71	106.9	O24—C25—H251	111.6
C7—C8—C9	113.82 (9)	H252—C25—H251	111.3
C7—C8—C17	100.10 (8)	O24—C25—H253	109.7
C9—C8—C17	111.97 (10)	H252—C25—H253	109.9
C7—C8—C26	111.19 (10)	H251—C25—H253	109.4
C9—C8—C26	112.11 (9)	C8—C26—C27	114.35 (9)
C17—C8—C26	106.84 (9)	C8—C26—H261	109.8
C8—C9—C10	123.88 (11)	C27—C26—H261	107.8
C8—C9—H91	116.5	C8—C26—H262	108.5
C10—C9—H91	119.6	C27—C26—H262	108.9
C1—C10—C9	120.09 (11)	H261—C26—H262	107.2
C1—C10—H101	119.9	C26—C27—O28	121.62 (10)
C9—C10—H101	120.0	C26—C27—N29	116.67 (10)
C7—O11—C12	106.08 (9)	O28—C27—N29	121.71 (11)
O11—C12—C13	123.20 (11)	C27—N29—C30	117.81 (11)
O11—C12—C17	114.38 (9)	C27—N29—C31	123.64 (11)
C13—C12—C17	122.32 (11)	C30—N29—C31	116.58 (11)
C12—C13—C14	116.83 (11)	N29—C30—H301	109.2
C12—C13—O24	116.83 (11)	N29—C30—H302	111.8
C14—C13—O24	126.34 (10)	H301—C30—H302	107.5
C13—C14—C15	120.82 (11)	N29—C30—H303	109.1
C13—C14—H141	121.3	H301—C30—H303	109.5
C15—C14—H141	117.9	H302—C30—H303	109.8
C14—C15—C16	121.42 (12)	N29—C31—H311	110.1
C14—C15—H151	120.2	N29—C31—H312	109.7
C16—C15—H151	118.4	H311—C31—H312	104.9
C15—C16—C17	117.62 (12)	N29—C31—H313	111.6
C15—C16—H161	121.3	H311—C31—H313	109.7
C17—C16—H161	121.1	H312—C31—H313	110.6

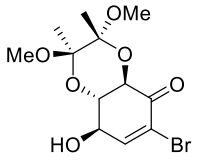
C3—O2—C1—C6	53.84 (13)	C18—C3—C4—O22	53.14 (14)
C3—O2—C1—C10	172.47 (10)	O5—C6—C7—C8	−178.81 (9)
C1—O2—C3—C4	−53.39 (14)	O5—C6—C7—O11	63.60 (12)

C1—O2—C3—C18	−175.78 (10)	C1—C6—C7—C8	−58.20 (12)
C1—O2—C3—O19	61.03 (13)	C1—C6—C7—O11	−175.79 (10)
C6—O5—C4—C21	179.51 (10)	C6—C7—C8—C26	149.31 (10)
C6—O5—C4—O22	56.62 (13)	O11—C7—C8—C26	−91.44 (11)
C4—O5—C6—C1	58.57 (12)	C6—C7—C8—C9	21.54 (13)
C4—O5—C6—C7	177.73 (9)	O11—C7—C8—C17	21.19 (12)
C6—O5—C4—C3	−57.59 (13)	C6—C7—C8—C17	−98.07 (11)
C12—O11—C7—C8	−20.71 (12)	O11—C7—C8—C9	140.80 (10)
C12—O11—C7—C6	99.71 (11)	C7—C8—C9—C10	7.82 (17)
C7—O11—C12—C13	−172.05 (11)	C17—C8—C9—C10	120.46 (13)
C7—O11—C12—C17	11.61 (14)	C9—C8—C26—C27	61.87 (14)
C20—O19—C3—O2	64.44 (15)	C17—C8—C26—C27	−175.11 (11)
C20—O19—C3—C4	−177.14 (11)	C7—C8—C17—C12	−14.64 (13)
C20—O19—C3—C18	−53.76 (16)	C9—C8—C17—C16	49.92 (18)
C23—O22—C4—C21	−57.28 (16)	C26—C8—C17—C12	101.31 (12)
C23—O22—C4—C3	178.73 (11)	C26—C8—C9—C10	−119.47 (13)
C23—O22—C4—O5	60.85 (15)	C26—C8—C17—C16	−73.19 (17)
C25—O24—C13—C12	−160.41 (12)	C7—C8—C26—C27	−66.81 (13)
C25—O24—C13—C14	18.8 (2)	C9—C8—C17—C12	−135.58 (11)
C31—N29—C27—C26	−15.2 (2)	C7—C8—C17—C16	170.86 (14)
C31—N29—C27—O28	165.31 (15)	C8—C9—C10—C1	0.94 (19)
C30—N29—C27—C26	−178.67 (13)	O11—C12—C13—O24	1.00 (18)
C30—N29—C27—O28	1.8 (2)	C13—C12—C17—C16	1.5 (2)
C6—C1—C10—C9	−37.52 (16)	O11—C12—C13—C14	−178.32 (12)
C10—C1—C6—O5	−175.26 (10)	C17—C12—C13—O24	177.05 (12)
O2—C1—C10—C9	−158.07 (12)	O11—C12—C17—C16	177.92 (11)
C10—C1—C6—C7	65.81 (13)	C17—C12—C13—C14	−2.27 (19)
O2—C1—C6—O5	−54.94 (13)	O11—C12—C17—C8	2.76 (15)
O2—C1—C6—C7	−173.86 (10)	C13—C12—C17—C8	−173.61 (11)
O19—C3—C4—O22	176.83 (9)	O24—C13—C14—C15	−178.18 (13)
O19—C3—C4—C21	53.13 (14)	C12—C13—C14—C15	1.1 (2)
O19—C3—C4—O5	−64.66 (12)	C13—C14—C15—C16	0.9 (2)
O2—C3—C4—O22	−64.47 (12)	C14—C15—C16—C17	−1.6 (2)
O2—C3—C4—C21	171.83 (11)	C15—C16—C17—C12	0.5 (2)
C18—C3—C4—C21	−70.56 (16)	C15—C16—C17—C8	174.35 (13)
O2—C3—C4—O5	54.04 (14)	C8—C26—C27—O28	4.57 (19)
C18—C3—C4—O5	171.65 (11)	C8—C26—C27—N29	−174.93 (12)

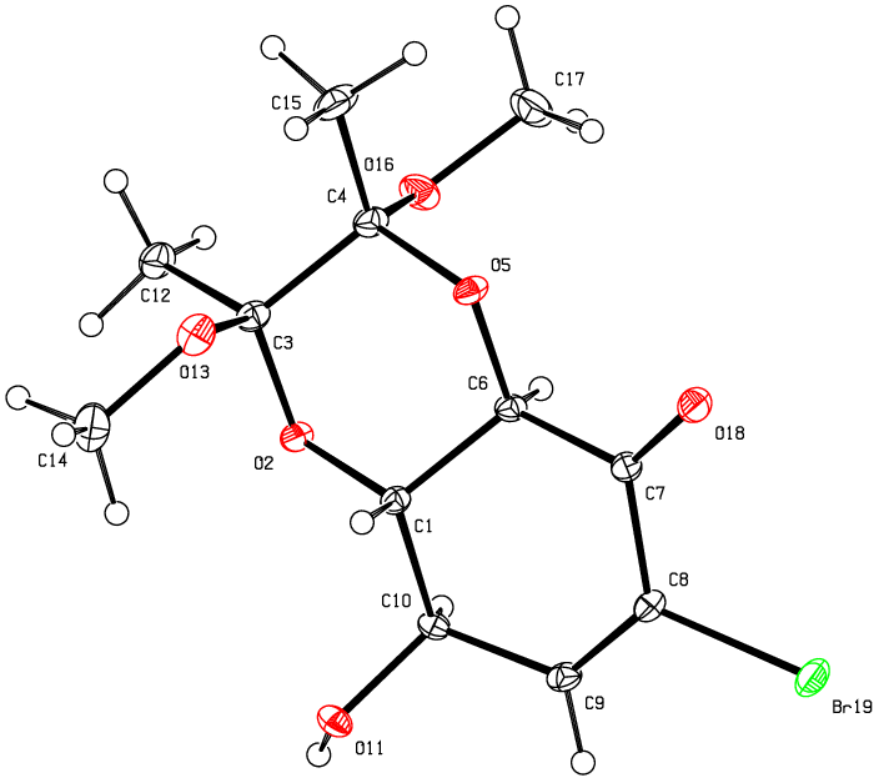
Symmetry codes: (i) −*x*+1, *y*−1/2, −*z*; (ii) −*x*+2, *y*−1/2, −*z*+1; (iii) −*x*+1, *y*+1/2, −*z*; (iv) *x*+1, *y*, *z*; (v) −*x*+1, *y*−1/2, −*z*+1.

Appendix Three

Single-crystal x-ray report for compound **9** of **publication 4**.



9



CCDC Deposition Number: **1491822**

Crystal structure of $C_{12}H_{17}BrO_6$ — banBDS_20

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Abstract

The crystal structure of $C_{12}H_{17}BrO_6$ is reported.

1. Comment

The crystallographic asymmetric unit consists of one molecule of $C_{12}H_{17}BrO_6$.

2. Synthesis and crystallization

The compound was prepared by JNB and recrystallized from a mixture of dichloromethane and ether. The sample code is JNB-10–71.

Related literature

Computing details

Data collection: SuperNova, (Oxford Diffraction, 2010); cell refinement: *CrysAlis PRO* (Agilent Technologies, 2015); data reduction: *CrysAlis PRO* (Agilent Technologies, 2015); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek, 2014); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

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(global)

Crystal data

$C_{12}H_{17}BrO_6$
$M_r = 337.17$
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
$a = 6.8265$ (1) Å
$b = 11.4217$ (1) Å
$c = 17.8288$ (1) Å
$V = 1390.12$ (1) Å^3
$Z = 4$
$F(000) = 688$
$D_x = 1.611$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å

Cell parameters from 16319 reflections
θ = 5–72°
μ = 4.23 mm^{-1}
T = 150 K
Rod, colourless
0.36 × 0.08 × 0.06 mm

Data collection

Oxford Diffraction SuperNova diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *CrysAlis PRO*, (Agilent, 2011)
T_{min} = 0.59, T_{max} = 0.79
21899 measured reflections
2750 independent reflections
2718 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.033
θ_{max} = 72.3°, θ_{min} = 4.6°
h = −8→6
k = −13→14
l = −22→21

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.021
$wR(F^2)$ = 0.052
S = 1.03
2750 reflections
176 parameters
1 restraint
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H atoms treated by a mixture of independent and constrained refinement
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.03P)^2 + 0.47P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}
Absolute structure: Flack (1983), 1145 Friedel-pairs
Absolute structure parameter: −0.029 (13)

Special details

Refinement

The absolute configuration of banBDS_20 (JNB-10–71) has been determined by refinement of the Flack parameter: The final value of the Flack parameter is −0.029 (13) and the final value of the Hooft parameter is −0.035 (6). This outcome is consistent with the absolute configuration of JNB-10–71 derived from *L*-(+)-tartaric acid. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, O—H = 0.82).

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.9839 (2)	0.32712 (15)	0.60420 (9)	0.0149
O2	1.02312 (17)	0.43547 (11)	0.64152 (7)	0.0172
C3	0.8589 (3)	0.51165 (16)	0.64438 (10)	0.0182
C4	0.6790 (3)	0.44894 (16)	0.68021 (11)	0.0197
O5	0.64725 (17)	0.33818 (11)	0.64304 (7)	0.0181
C6	0.8186 (2)	0.26667 (15)	0.64519 (10)	0.0158
C7	0.7711 (3)	0.14662 (15)	0.61424 (9)	0.0166
C8	0.9503 (3)	0.07926 (16)	0.59490 (9)	0.0185
C9	1.1272 (3)	0.12686 (16)	0.59088 (9)	0.0188
C10	1.1700 (2)	0.25441 (16)	0.60666 (10)	0.0157
O11	1.30406 (18)	0.29865 (12)	0.55292 (7)	0.0198
C12	0.9259 (3)	0.61621 (16)	0.69049 (11)	0.0246
O13	0.7956 (2)	0.54277 (12)	0.57173 (8)	0.0251
C14	0.9425 (4)	0.59328 (19)	0.52527 (11)	0.0340
C15	0.4894 (3)	0.5161 (2)	0.67214 (15)	0.0339
O16	0.7343 (2)	0.42867 (13)	0.75536 (7)	0.0259
C17	0.5935 (4)	0.3690 (2)	0.80089 (12)	0.0370
O18	0.60616 (19)	0.10912 (11)	0.60961 (8)	0.0244

Br19	0.91184 (3)	−0.082495 (16)	0.576343 (13)	0.0292
H11	0.9466	0.3404	0.5516	0.0180*
H61	0.8622	0.2552	0.6973	0.0186*
H91	1.2327	0.0815	0.5782	0.0235*
H101	1.2280	0.2614	0.6565	0.0195*
H123	0.8244	0.6767	0.6909	0.0368*
H121	1.0471	0.6477	0.6711	0.0376*
H122	0.9485	0.5920	0.7415	0.0371*
H141	0.8854	0.6076	0.4776	0.0526*
H143	1.0536	0.5434	0.5177	0.0520*
H142	0.9861	0.6673	0.5450	0.0517*
H152	0.3843	0.4690	0.6917	0.0503*
H151	0.4646	0.5333	0.6201	0.0501*
H153	0.4973	0.5905	0.6999	0.0506*
H172	0.6618	0.3333	0.8431	0.0570*
H173	0.5326	0.3074	0.7721	0.0559*
H171	0.4963	0.4214	0.8199	0.0566*
H111	1.411 (3)	0.304 (2)	0.5731 (13)	0.0296*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0141 (7)	0.0143 (8)	0.0162 (7)	0.0007 (6)	−0.0011 (6)	−0.0022 (6)
O2	0.0133 (5)	0.0165 (6)	0.0217 (6)	−0.0002 (5)	−0.0018 (4)	−0.0047 (5)
C3	0.0181 (8)	0.0175 (9)	0.0190 (8)	0.0017 (7)	−0.0015 (6)	−0.0040 (7)
C4	0.0171 (8)	0.0182 (9)	0.0238 (8)	−0.0013 (7)	−0.0001 (7)	−0.0083 (7)
O5	0.0124 (5)	0.0158 (6)	0.0263 (6)	0.0010 (4)	−0.0022 (4)	−0.0074 (5)
C6	0.0118 (7)	0.0173 (8)	0.0182 (8)	0.0010 (6)	−0.0005 (6)	−0.0022 (6)
C7	0.0147 (8)	0.0168 (8)	0.0183 (8)	0.0017 (7)	−0.0008 (6)	0.0013 (6)
C8	0.0197 (8)	0.0147 (8)	0.0212 (8)	0.0035 (7)	−0.0014 (6)	0.0000 (6)
C9	0.0163 (8)	0.0193 (8)	0.0208 (8)	0.0058 (7)	−0.0006 (6)	0.0009 (6)
C10	0.0105 (7)	0.0198 (8)	0.0169 (7)	−0.0001 (6)	0.0000 (6)	0.0000 (6)
O11	0.0131 (6)	0.0252 (7)	0.0211 (6)	−0.0016 (5)	0.0016 (5)	0.0020 (5)
C12	0.0256 (9)	0.0198 (8)	0.0285 (9)	−0.0030 (8)	0.0001 (8)	−0.0084 (7)
O13	0.0292 (7)	0.0239 (6)	0.0223 (6)	0.0020 (5)	−0.0069 (6)	0.0009 (5)
C14	0.0529 (13)	0.0239 (10)	0.0252 (9)	−0.0056 (10)	0.0019 (9)	0.0001 (8)
C15	0.0198 (9)	0.0221 (11)	0.0596 (15)	0.0057 (8)	−0.0014 (9)	−0.0128 (10)
O16	0.0270 (7)	0.0313 (7)	0.0194 (6)	−0.0064 (6)	0.0058 (5)	−0.0069 (5)
C17	0.0397 (12)	0.0367 (11)	0.0347 (10)	−0.0108 (11)	0.0194 (10)	−0.0084 (9)
O18	0.0164 (6)	0.0187 (6)	0.0383 (7)	−0.0015 (5)	0.0002 (6)	−0.0028 (5)
Br19	0.02357 (10)	0.01437 (9)	0.04966 (12)	0.00161 (7)	0.00073 (9)	−0.00332 (8)

Geometric parameters (Å, º)

C1—O2	1.430 (2)	C9—H91	0.916
C1—C6	1.511 (2)	C10—O11	1.418 (2)
C1—C10	1.518 (2)	C10—H101	0.976
C1—H11	0.983	O11—H111	0.815 (16)
O2—C3	1.420 (2)	C12—H123	0.978
C3—C4	1.558 (2)	C12—H121	0.966
C3—C12	1.520 (2)	C12—H122	0.963
C3—O13	1.411 (2)	O13—C14	1.423 (3)

C4—O5	1.445 (2)	C14—H141	0.949
C4—C15	1.512 (3)	C14—H143	0.958
C4—O16	1.411 (2)	C14—H142	0.963
O5—C6	1.427 (2)	C15—H152	0.963
C6—C7	1.513 (2)	C15—H151	0.963
C6—H61	0.984	C15—H153	0.984
C7—C8	1.486 (2)	O16—C17	1.431 (2)
C7—O18	1.207 (2)	C17—H172	0.975
C8—C9	1.327 (3)	C17—H173	0.966
C8—Br19	1.8951 (19)	C17—H171	0.955
C9—C10	1.512 (3)		

O2—C1—C6	108.07 (13)	C10—C9—H91	116.1
O2—C1—C10	107.64 (13)	C1—C10—C9	111.09 (14)
C6—C1—C10	111.16 (14)	C1—C10—O11	109.00 (14)
O2—C1—H11	111.0	C9—C10—O11	110.01 (14)
C6—C1—H11	109.7	C1—C10—H101	108.7
C10—C1—H11	109.2	C9—C10—H101	109.1
C1—O2—C3	113.51 (12)	O11—C10—H101	108.9
O2—C3—C4	110.80 (15)	C10—O11—H111	107.8 (18)
O2—C3—C12	105.25 (15)	C3—C12—H123	110.2
C4—C3—C12	112.12 (15)	C3—C12—H121	110.9
O2—C3—O13	111.29 (14)	H123—C12—H121	110.3
C4—C3—O13	104.54 (14)	C3—C12—H122	109.5
C12—C3—O13	112.99 (15)	H123—C12—H122	108.1
C3—C4—O5	109.44 (15)	H121—C12—H122	107.9
C3—C4—C15	113.74 (16)	C3—O13—C14	114.89 (15)
O5—C4—C15	105.79 (15)	O13—C14—H141	107.6
C3—C4—O16	104.71 (14)	O13—C14—H143	113.5
O5—C4—O16	109.39 (15)	H141—C14—H143	107.6
C15—C4—O16	113.75 (17)	O13—C14—H142	111.1
C4—O5—C6	111.46 (13)	H141—C14—H142	107.6
C1—C6—O5	109.72 (14)	H143—C14—H142	109.2
C1—C6—C7	113.43 (14)	C4—C15—H152	108.7
O5—C6—C7	109.46 (14)	C4—C15—H151	110.2
C1—C6—H61	106.9	H152—C15—H151	109.4
O5—C6—H61	110.5	C4—C15—H153	110.1
C7—C6—H61	106.8	H152—C15—H153	110.0
C6—C7—C8	112.18 (15)	H151—C15—H153	108.5
C6—C7—O18	123.10 (16)	C4—O16—C17	115.92 (16)
C8—C7—O18	124.62 (16)	O16—C17—H172	108.4
C7—C8—C9	123.36 (17)	O16—C17—H173	109.5
C7—C8—Br19	115.56 (13)	H172—C17—H173	108.1
C9—C8—Br19	121.07 (13)	O16—C17—H171	111.7
C8—C9—C10	124.10 (16)	H172—C17—H171	108.7
C8—C9—H91	119.8	H173—C17—H171	110.3

Hydrogen-bond geometry (Å, º)

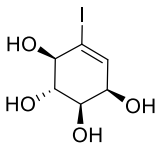
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C17—H171···O18^{i}	0.96	2.58	3.453 (3)	152 (1)

O11—H111···O5^{ii}	0.82	2.08	2.877 (3)	167 (3)

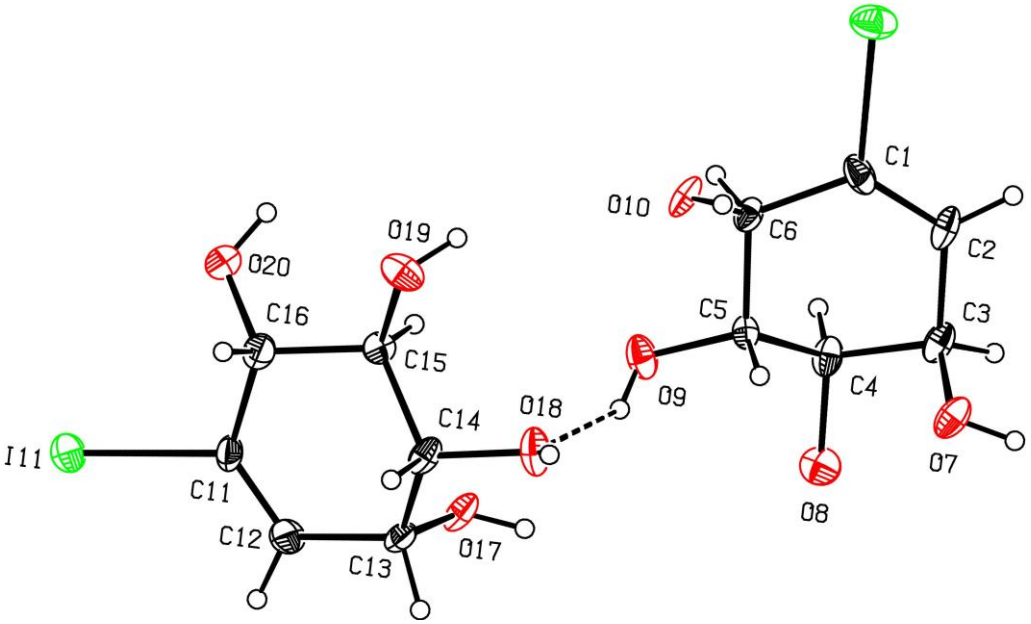
Symmetry codes: (i) $-x+1, y+1/2, -z+3/2$; (ii) $x+1, y, z$.

Appendix Four

Single-crystal X-ray report for compound **14** of **publication 5**.



14



CCDC Deposition Number: **1533559**

Structure report on compound BAN16_PC50SN (jnb-11–79-2) $C_6H_9O_4I$

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Abstract

The structure of the title compound, $C_6H_9O_4I$, is reported. Data were collected at 150 K and exhibited monoclinic ($P2_1$) symmetry with two molecules within the asymmetric unit. The diffraction data were of relatively poor quality (R_{int}=0.13) and a filter was applied that excluded all data frames with R_{int} values compared to the rest of the data set in excess of 0.30. This was probably in part due due to the fact that the crystal was a long thin plate with anisotropic absorption of X-rays. Despite the poor data, the structure refined to give a well resolved structure with a final *R*-factor of 0.081. Residual difference electron density maxima were observed close to the iodine atoms, which is most likely the effect of Fourier series truncation ripples caused by excluded data being absent. The absolute configuration is established. The Flack parameter refined to a value of −0.041 (19). Hydrogen atoms were constrained to riding geometry except for H9 that forms a hydrogen bond to O18, which was allowed to refine freely.

1. Introduction

2. Experimental

Crystal data, data collection and structure refinement details are summarized in Table 1.

3. Results and discussion

Table 1

Experimental details

Crystal data	
Chemical formula	$C_6H_9IO_4$
M_r	272.03
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	150
a, *b*, *c* (Å)	9.4654 (3), 7.09196 (19), 13.2976 (5)
β (°)	110.611 (4)
V (Å^3)	835.51 (5)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	29.91
Crystal size (mm)	0.46 × 0.14 × 0.04
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, EosS2
Absorption correction	For a sphere *CrysAlis PRO* 1.171.38.43 (Rigaku Oxford Diffraction, 2015) Spherical absorption correction using equivalent radius and absorption coefficient. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.048, 0.144

No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	14260, 3355, 3304
R_{int}	0.130
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.623
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.081, 0.225, 1.05
No. of reflections	3355
No. of parameters	210
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	4.27, −1.99
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Absolute structure parameter	−0.041 (19)

Computer programs: *CrysAlis PRO* 1.171.38.43 (Rigaku OD, 2015), *SHELXT* (Sheldrick, 2015), *SHELXL97* (Sheldrick, 2015), SHELXLE (C. B. Hubschle *et al.*, 2011), *publCIF* (Westrip, 2010).

Acknowledgements

References

Agilent (2014). *CrysAlis PRO*. Agilent Technologies Ltd, Yarnton, Oxfordshire, England.

Hubschle, C. B., Sheldrick, G. M. & Dittrich, B. (2011). ′ShelXle: a Qt graphical user interface for *SHELXL*′ J. Appl. Cryst. 44, 1281-1284 .

Sheldrick, G. M. (2015). *Acta Cryst.* A**71**, 3–8.

Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.

Figure 1

Contents of the asymmetric unit shown with displacement ellipsoids drawn at the 30% probability level. H atoms are drawn as spheres of arbitrary radius.

supporting information

Structure report on compound BAN16_PC50SN (jnb-11–79-2) $C_6H_9O_4I$

Computing details

Data collection: *CrysAlis PRO* 1.171.38.43 (Rigaku OD, 2015); cell refinement: *CrysAlis PRO* 1.171.38.43 (Rigaku OD, 2015); data reduction: *CrysAlis PRO* 1.171.38.43 (Rigaku OD, 2015); program(s) used to solve structure: *SHELXT* (Sheldrick, 2015); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2015); molecular graphics: SHELXLE (C. B. Hubschle *et al.*, 2011); software used to prepare material for publication: *publCIF* (Westrip, 2010).

(ban16_pc50sn)

Crystal data

$C_6H_9IO_4$
$M_r = 272.03$
Monoclinic, $P2_1$
Hall symbol: P 2yb
$a = 9.4654$ (3) Å
$b = 7.09196$ (19) Å
$c = 13.2976$ (5) Å
$\beta = 110.611$ (4)°
$V = 835.51$ (5) Å^3
$Z = 4$
$F(000) = 520$
$D_x = 2.163$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å
Cell parameters from 10373 reflections
$\theta = 3.5$–$73.6°$
$\mu = 29.91$ mm^{-1}
$T = 150$ K
Plate, colourless
0.46 × 0.14 × 0.04 mm

Data collection

SuperNova, Dual, Cu at zero, EosS2 diffractometer
Radiation source: micro-focus sealed X-ray tube, SuperNova (Cu) X-ray Source
Mirror monochromator
Detector resolution: 8.1297 pixels mm^{-1}
ω scans
Absorption correction: for a sphere *CrysAlis PRO* 1.171.38.43 (Rigaku Oxford Diffraction, 2015) Spherical absorption correction using equivalent radius and absorption coefficient. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
$T_{min} = 0.048$, $T_{max} = 0.144$
14260 measured reflections
3355 independent reflections
3304 reflections with $I > 2\sigma(I)$
$R_{int} = 0.130$
$\theta_{max} = 73.9°$, $\theta_{min} = 3.6°$
$h = -9 \rightarrow 11$
$k = -8 \rightarrow 8$
$l = -16 \rightarrow 15$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.081$
$wR(F^2) = 0.225$
$S = 1.05$
3355 reflections
210 parameters
1 restraint
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1805P)^2 + 5.057P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 4.27$ e Å^{-3}
$\Delta\rho_{min} = -1.99$ e Å^{-3}

Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881

Absolute structure parameter: −0.041 (19)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.0607 (15)	0.692 (2)	0.2300 (10)	0.036 (3)
I1	−0.07981 (10)	0.52737 (14)	0.10332 (7)	0.0459 (3)
C3	0.1726 (15)	1.0051 (19)	0.3108 (12)	0.034 (3)
H3	0.2190	1.1086	0.2817	0.041*
C2	0.0721 (15)	0.8769 (17)	0.2178 (12)	0.032 (3)
H2	0.0174	0.9326	0.1503	0.039*
C4	0.2962 (14)	0.8800 (17)	0.3886 (11)	0.031 (2)
H4	0.3652	0.8315	0.3523	0.037*
C5	0.2222 (12)	0.7174 (16)	0.4248 (9)	0.025 (2)
H5	0.1457	0.7661	0.4543	0.030*
C6	0.1471 (13)	0.5856 (16)	0.3304 (10)	0.027 (2)
H6	0.2289	0.5138	0.3160	0.033*
O7	0.0806 (10)	1.0822 (13)	0.3669 (9)	0.036 (2)
H7	0.0567	1.1936	0.3466	0.054*
O8	0.3789 (11)	0.9986 (15)	0.4788 (8)	0.038 (2)
H8	0.4634	1.0258	0.4751	0.058*
O9	0.3379 (11)	0.6126 (16)	0.5067 (8)	0.037 (2)
H9	0.325 (14)	0.63 (2)	0.564 (11)	0.01 (3)*
O10	0.0570 (10)	0.4537 (12)	0.3603 (9)	0.0338 (19)
H10	−0.0301	0.4980	0.3464	0.051*
I11	0.67347 (10)	−0.07331 (13)	0.93968 (7)	0.0415 (3)
C12	0.5406 (16)	0.310 (2)	0.8721 (11)	0.038 (3)
H12	0.6141	0.3446	0.9392	0.046*
C13	0.4418 (14)	0.4583 (16)	0.8040 (10)	0.028 (2)
H13	0.4225	0.5574	0.8511	0.033*
C14	0.2900 (14)	0.3794 (16)	0.7286 (11)	0.029 (2)
H14	0.2281	0.3400	0.7724	0.035*
C15	0.3189 (12)	0.2075 (17)	0.6691 (9)	0.025 (2)
H15	0.3795	0.2485	0.6247	0.030*
C16	0.4058 (15)	0.0504 (19)	0.7457 (10)	0.032 (2)
H16	0.3335	−0.0186	0.7722	0.039*
O17	0.5229 (11)	0.5406 (12)	0.7414 (8)	0.0350 (19)
H17	0.4827	0.6437	0.7155	0.052*
O18	0.2137 (11)	0.5231 (17)	0.6575 (8)	0.039 (2)
H18	0.1237	0.5281	0.6546	0.059*
O19	0.1771 (10)	0.1345 (17)	0.5986 (8)	0.037 (2)
H19	0.1589	0.1770	0.5364	0.056*

O20	0.4696 (12)	−0.0801 (16)	0.6938 (8)	0.041 (2)
H20	0.4222	−0.0764	0.6273	0.061*
C11	0.5289 (15)	0.1366 (19)	0.8422 (11)	0.034 (3)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.028 (6)	0.050 (8)	0.026 (6)	0.015 (6)	0.005 (5)	0.009 (6)
I1	0.0336 (5)	0.0575 (6)	0.0396 (5)	0.0009 (4)	0.0044 (3)	−0.0157 (4)
C3	0.036 (6)	0.020 (5)	0.051 (7)	−0.002 (5)	0.020 (6)	0.005 (5)
C2	0.030 (6)	0.019 (5)	0.055 (8)	0.004 (4)	0.023 (6)	0.011 (5)
C4	0.024 (5)	0.025 (6)	0.043 (7)	−0.004 (4)	0.012 (5)	0.008 (5)
C5	0.022 (5)	0.024 (5)	0.026 (5)	0.000 (4)	0.006 (4)	0.006 (4)
C6	0.020 (5)	0.021 (5)	0.036 (6)	0.001 (4)	0.003 (4)	0.001 (4)
O7	0.030 (4)	0.022 (4)	0.060 (6)	−0.003 (3)	0.021 (4)	0.000 (4)
O8	0.036 (5)	0.040 (5)	0.041 (5)	−0.016 (4)	0.016 (4)	−0.002 (4)
O9	0.029 (4)	0.048 (5)	0.035 (5)	0.013 (4)	0.011 (4)	0.015 (4)
O10	0.033 (4)	0.014 (4)	0.059 (6)	0.005 (3)	0.021 (4)	0.002 (4)
I11	0.0384 (5)	0.0420 (5)	0.0359 (5)	0.0082 (4)	0.0028 (3)	0.0027 (4)
C12	0.031 (6)	0.040 (7)	0.032 (6)	0.009 (6)	−0.004 (5)	−0.004 (6)
C13	0.035 (6)	0.017 (5)	0.034 (6)	−0.002 (4)	0.014 (5)	−0.004 (4)
C14	0.026 (6)	0.023 (6)	0.047 (7)	0.006 (4)	0.023 (5)	0.001 (5)
C15	0.015 (5)	0.029 (6)	0.030 (6)	0.001 (4)	0.005 (4)	−0.002 (5)
C16	0.037 (6)	0.028 (6)	0.036 (6)	0.003 (5)	0.017 (5)	0.003 (5)
O17	0.043 (5)	0.016 (4)	0.054 (5)	0.000 (4)	0.026 (4)	0.000 (4)
O18	0.031 (4)	0.044 (5)	0.046 (5)	0.012 (4)	0.017 (4)	0.021 (5)
O19	0.021 (4)	0.055 (6)	0.031 (4)	−0.013 (4)	0.003 (4)	−0.004 (4)
O20	0.055 (6)	0.029 (4)	0.037 (5)	0.001 (5)	0.014 (4)	−0.003 (4)
C11	0.036 (6)	0.023 (6)	0.033 (6)	0.005 (5)	0.000 (5)	0.006 (5)

Geometric parameters (Å, º)

C1—C2	1.33 (2)	I11—C11	2.126 (13)
C1—C6	1.500 (17)	C12—C11	1.29 (2)
C1—I1	2.096 (16)	C12—C13	1.482 (19)
C3—O7	1.440 (16)	C12—H12	0.9500
C3—C4	1.540 (18)	C13—O17	1.440 (14)
C3—C2	1.56 (2)	C13—C14	1.538 (18)
C3—H3	1.0000	C13—H13	1.0000
C2—H2	0.9500	C14—O18	1.405 (16)
C4—O8	1.449 (17)	C14—C15	1.530 (15)
C4—C5	1.513 (14)	C14—H14	1.0000
C4—H4	1.0000	C15—O19	1.436 (13)
C5—O9	1.448 (14)	C15—C16	1.539 (17)
C5—C6	1.525 (16)	C15—H15	1.0000
C5—H5	1.0000	C16—O20	1.411 (16)
C6—O10	1.413 (14)	C16—C11	1.525 (19)
C6—H6	1.0000	C16—H16	1.0000
O7—H7	0.8400	O17—H17	0.8400
O8—H8	0.8400	O18—H18	0.8400
O9—H9	0.82 (13)	O19—H19	0.8400
O10—H10	0.8400	O20—H20	0.8400

C2—C1—C6	124.2 (14)	C11—C12—C13	121.4 (13)
C2—C1—I1	120.4 (11)	C11—C12—H12	119.3
C6—C1—I1	115.4 (10)	C13—C12—H12	119.3
O7—C3—C4	109.0 (11)	O17—C13—C12	106.8 (11)
O7—C3—C2	108.7 (10)	O17—C13—C14	109.7 (10)
C4—C3—C2	107.7 (10)	C12—C13—C14	112.6 (10)
O7—C3—H3	110.5	O17—C13—H13	109.2
C4—C3—H3	110.5	C12—C13—H13	109.2
C2—C3—H3	110.5	C14—C13—H13	109.2
C1—C2—C3	122.0 (13)	O18—C14—C15	111.9 (11)
C1—C2—H2	119.0	O18—C14—C13	108.4 (10)
C3—C2—H2	119.0	C15—C14—C13	109.3 (9)
O8—C4—C5	110.8 (10)	O18—C14—H14	109.1
O8—C4—C3	106.5 (10)	C15—C14—H14	109.1
C5—C4—C3	109.0 (10)	C13—C14—H14	109.1
O8—C4—H4	110.2	O19—C15—C14	109.2 (9)
C5—C4—H4	110.2	O19—C15—C16	109.2 (10)
C3—C4—H4	110.2	C14—C15—C16	112.7 (10)
O9—C5—C4	108.6 (9)	O19—C15—H15	108.6
O9—C5—C6	108.3 (10)	C14—C15—H15	108.6
C4—C5—C6	109.8 (10)	C16—C15—H15	108.6
O9—C5—H5	110.0	O20—C16—C11	110.0 (11)
C4—C5—H5	110.0	O20—C16—C15	111.8 (10)
C6—C5—H5	110.0	C11—C16—C15	109.8 (11)
O10—C6—C1	112.9 (11)	O20—C16—H16	108.4
O10—C6—C5	109.1 (10)	C11—C16—H16	108.4
C1—C6—C5	112.0 (10)	C15—C16—H16	108.4
O10—C6—H6	107.5	C13—O17—H17	109.5
C1—C6—H6	107.5	C14—O18—H18	109.5
C5—C6—H6	107.5	C15—O19—H19	109.5
C3—O7—H7	109.5	C16—O20—H20	109.5
C4—O8—H8	109.5	C12—C11—C16	126.9 (13)
C5—O9—H9	108 (10)	C12—C11—I11	121.0 (11)
C6—O10—H10	109.5	C16—C11—I11	111.7 (9)